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Recent Research on EMF and Health Risk

Seventh annual report from SSM:s Independent Expert Group on Electromagnetic Fields, 2010

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This report concerns a study which has been conducted for the Swedish Radiation Safety Authority, SSM. The conclusions and viewpoints presented in the report are those of the author/authors and do not necessarily coincide with those of the SSM.

Contents

Preface

In 2002, the Swedish Radiation Protection Authority, SSI (Statens strålskyddsinstitut) appointed an international independent expert group (IEG) for electromagnetic fields (EMF) and health. The Swedish government has reorganized the radiation protection work and the task of the IEG lie now under the newly formed Swedish Radiation Safety Authority (SSM). The task is to follow and evaluate the scientific development and to give advice to the SSM. With major scientific reviews as starting points the IEG in a series of annual reports consecutively discusses and assesses relevant new data and put these in the context of already available information. The result will be a gradually developing health risk assessment of exposure to EMF. The group began its work in the fall of 2002 and presented its first report in December 2003. The present report is the seventh in the series.

The composition of the group during the preparation of this report has been:

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Declarations of conflicts of interest are available at SSM.

Stockholm in December 2010

Anders Ahlbom

Chair

Update on key issues

ELF magnetic fields (of the type that emanates from distribution and use of electricity) are associated with an increased risk of childhood leukaemia in epidemiologic research and have been classified as a possible carcinogen to humans by IARC (WHO's International Agency for Research on Cancer). While most research was done one and two decades ago, the association has been confirmed in recent studies. However, experimental and mechanistic research has been unable to find an explanation for this association. Thus, this remains a rather intriguing issue. Particularly during the 1980's and early 1990's a large number of diseases were studied in relation to ELF but mostly without consistent associations being found. One of those diseases was Alzheimer's for which current studies have generated a renewed interest because associations have been reported both in environmental and occupational studies. A causal relationship has not been established, however.

This year has seen the publication of the long awaited Interphone study looking at brain tumour risk in mobile phone users. However, the advent of these new data does not change the overall picture being that for up to about ten years of mobile phone use associations with brain tumour risk are unlikely. This conclusion is based on the collective of studies on mobile phone use and brain tumour risk as well as on overall trends (rather lack thereof) in brain tumour statistics. For longer duration of use, for specific subtypes of cancer, and for children and adolescents data are sparse or non-existing, and conclusions are less certain.

Available data do not indicate any risks related to exposure to RF from base stations or radio or TV antennas. Taking into account also the low levels of exposure that these sources give rise to, health effects from transmitters are unlikely.

While heating remains the only established biological effect from exposure to RF fields, the studies on human volunteers showing effects on EEG in the alpha band are rather interesting and certainly warrant further study. The effects are weak and not associated with any behavioural or health consequences. However, they appear to be mediated by a mechanism other than heating.

Executive Summary

ELF (extremely low frequency) fields

Cell studies

Many new findings have been published in the last years on ELF magnetic field bioeffects. Most of the *in-vitro* studies are dealing with DNA damage, production of Reactive Oxygen Species (ROS) and expression of genes. They are mostly uncorrelated in terms of cell models and endpoints and performed under high-level exposure, i.e., in the millitesla range. Moreover, most of the *in-vitro* studies are not addressing directly the most critical issues, which are mechanistic explanations for the association between ELF exposure and childhood leukaemia.

The conclusion on genotoxic effects is that the differences between ELF-exposed and sham-exposed cells have been small with little biological relevance (although statistically significant in some studies). The trend is toward more studies performed with combined exposure to ELF magnetic fields and chemical or physical agents. This may help resolve the current uncertainty about the causality of the link between ELF exposure and childhood leukaemia in that a synergy with another agent might be needed for the ELF magnetic fields to affect leukemic processes.

Animal studies

The question of whether ELF magnetic fields have any influence on the development of acute lymphoblastic leukaemia (ALL) in children still remains unresolved. Although a rat ALL model was developed, it was only applied in adult animals. Moreover, only small groups were used, which made it virtually impossible to perform any proper statistical analyses. This has been a problem in several of the studies described. Another problem is the high incidence of disease in control groups, which hampered detection of relatively small effects. Animal studies have to use better designs in order to be useful for health risk analysis.

Epidemiology

For ELF magnetic fields and the risk of childhood leukaemia, the previous conclusion still holds: a consistent association has been observed, but a causal relationship has not been established. Evidence regarding breast cancer weighs against an increased risk. Little new information has become available concerning parental exposure and risk of childhood cancer. Some evidence for a possible association of Alzheimer's disease with ELF magnetic field exposure has been obtained and further research is warranted.

RF (radiofrequency) fields

Cell studies

The main endpoints investigated are DNA damage, production of ROS, expression of genes (HSP in particular) and effects on spermatozoa. No new non-thermal biological effects of RF exposure have been established. However, the number of ongoing studies on the effects of combined exposures (RF + chemical or physical agent) is increasing despite the current decrease in research funding.

Animal studies

Recent studies indicate that in rodents, long-term exposure to a relatively strong GSM mobile phone signal may result in a response in brain cells that indicates activation in response to injury. This might have an effect on memory and cognitive functions. In previous SSM reports some behavioural effects have been reported, but a clear dose-response relationship has not been established. It is still unclear whether and to what extent rodent behaviour can be influenced by RF exposure. No inferences at all can be made from these studies with respect to any influence on human behaviour.

A study on the effect of a GSM mobile phone signal on the development of Alzheimer's disease indicated a possible beneficial positive effect, but it needs to be replicated with an improved design and larger groups before any conclusions can be drawn. Again, any extrapolation to humans is premature and unwarranted.

In previous SSM reports it was concluded that RF EMF does not act as tumour inducer: there is no carcinogenic effect of exposure to RF EMF alone. In some, but not all, previously described studies RF EMF exposure was observed to enhance the incidence of tumours induced by other agents, i.e. exert a promoting effect. In a recent study this was also observed for exposure to a 3G base station signal, with a field strength higher than environmental exposures, but below the exposure limit. Without confirmation from other studies and with other species it is hard to conclude that this effect is real.

A multigeneration study on effects of a 3G base station signal on rodent development did not show any effects. This was also the case with a study employing two mobile telephone signals. These results are in accordance with previous conclusions that there does not seem to be an effect of non-thermal RF EMF on development.

It was noted that a considerable number of studies could not be evaluated because of design problems. Especially noteworthy is that often proper information on exposure is lacking. This is a waste of effort and resources. As was concluded with ELF EMF, animal studies have to use better designs in order to be useful for health risk analysis.

Human laboratory studies

During the last year a number of high-quality reports on the effects of mobile phone EMF on sleep quality parameters and sleep EEG have been published, helping to solve some of the questions produced by the previous, contradictory data. EEG studies again show effects of GSM mobile phone EMF (i.e. a pulsed signal) on the alpha-band while the corresponding non-pulsed signal did not produce such effects. This phenomenon should be further studied using well controlled experimental setups (in terms of dosimetry and EEG recording) with animal models and neural tissue cultures, in order to see how the electrical activity of neuronal networks is affected by the GSM and 3G signals (pulsed or non-pulsed). Imaging (e.g. PET) studies have shown promising, although variable, results possibly due to the differences between GSM and 3G signals. Further studies will need to be well-designed and have an adequate number of participants to obtain good statistical power. There are some modern neuroscientific methods (e.g. brain imaging and brain stimulation) that should be used to address the issue of perceived electrical hypersensitivity. Finally, comprehensive studies on long-term exposures, and especially studies on effects on children are still lacking.

Epidemiology

Based on the results from the pooled analyses of the INTERPHONE study and two studies evaluating data from high-quality cancer registries, an increase in the short-term risk of brain tumours due to mobile phone use can be excluded with a high degree of certainty. If mobile phone use increases brain tumour risk by 50% or more, one would roughly expect to observe an increase in the brain tumour incidence of 30% or more since the introduction of mobile

phones assuming a prevalence of mobile phone use of 60%. Such an increase would be clearly detectable unless it is compensated by a very strong preventive factor that was introduced at the same time as mobile phones. So far, nobody has suggested such a preventive factor. It is particularly hard to imagine that risk increases of 100% or more that have been reported in some studies for specific age groups would not be detectable in brain cancer incidence data.
A potential risk for a specific histological tumour entity would be harder to detect in time trends data as the number of cases is small and thus time trends are more fluctuating. Similarly, identification of a potential long-term effect is more challenging since the prevalence of long-term users is smaller. In particular, no data are available for very long exposure periods of more than 20 years. However, even if induction time is long on average, incident cases with shorter than average induction periods have to be expected, as the latency distribution will scatter around the mean induction time. Thus, if use of mobile phones was a substantial long term risk, incidence data should indicate increasing rates by now. Though, a small risk increase may still be undetectable.

Two studies on broadcast transmitters and cancer risk with reasonably good exposure assessments and other validity aspects were published in 2009, and have now been followed by the first full-scale epidemiologic study on mobile phone base stations and childhood cancer. No indications of associations were found with any of the proxies for exposure used in this study. In conclusion, based on this and on previous studies on transmitters and cancer one cannot exclude the existence of cancer risks with certainty, but so far no scientific data indicate the existence of such a risk.

Sammanfattning på svenska

Extremt lågfrekventa elektromagnetiska fält (ELF)

Cellstudier

Det har publicerats många studier under de senaste åren om biologiska effekter av ELF. De flesta har undersökt DNA skador, oxidativ stress eller genuttryck. De har dock i huvudsak varit oberoende av varandra vad avser cellmodeller och utfall och exponeringarna har varit i milliteslaområdet, det vill säga höga. Denna forskning har inte heller varit inriktad mot den mest kritiska frågeställningen nämligen ELF exponering och cancer.

Slutsatsen när det gäller genotoxiska effekter är att de har varit små och utan egentlig biologisk relevans, även om de varit statistiskt signifikanta. Utvecklingen går mot studier med kombinerad ELF exponering och kemisk eller annan fysikalisk exponering. Detta kan bidra till förståelse av sambandet mellan ELF och cancer eftersom det kan vara en synergistisk effekt som ligger bakom.

Djurstudier

En djurmodell för studier av akut lymfoblastisk leukemi (ALL) har utvecklats, men den har bara tillämpats på fullvuxna djur. De studier som finns har dessutom varit för små för habila statistiska analyser. Tumörincidensen i kontrollgrupperna har också varit hög vilket gjort det svårt att upptäcka skillnader mellan exponerade och oexponerade grupper. Följaktligen måste designen av djurstudierna förbättras för att de ska kunna bidra till riskanalysen.

Epidemiologiska studier

För ELF magnetiska fält gäller fortfarande den tidigare slutsatsen, nämligen det finns ett samband med risk för leukemi hos barn, men att det fortfarande inte går att avgöra om det är fråga om ett orsakssamband. När det gäller risk för bröstcancer så talar tillgängliga data emot ett samband med ELF. Ytterst lite nya data har kommit fram om föräldrars exponering och risk för sjukdom hos barnet. Vad gäller risk för Alzheimers sjukdom så finns det nya resultat både från omgivningsmiljö och arbetsmiljö som stärker hypotesen om ett samband med ELF och mer forskning inom detta område är påkallad.

Radiofrekventa elektromagnetiska fält (RF)

Cellstudier

De vanligaste utfallen i cellstudier av RF-exponering har varit DNA skada, oxidativ stress och genuttryck (särskilt så kallade heat shock protein) och effekter på spermaceller. Inga nya icke-termiska biologiska effekter av RF-exponering har upptäckts. Studier av kombinerade effekter, dvs RF tillsammans med någon kemisk eller annan fysikalisk exponering, ökar i försök att upptäcka eventuella synergistiska effekter.

Djurstudier

Nyare studier på råtta tyder på att långtidsexponering för GSM signaler kan leda till att hjärnceller aktiveras som de gör vid skada. Detta skulle kunna påverka minne och kognitionsförmåga. Detta har diskuterats i tidigare SSM rapporter men sambanden kan ännu inte uppfattas som fastställda och det förblir osäkert om och i så fall i vilken utsträckning som beteende hos råtta kan påverkas av RF exponering.

En undersökning tycks visa att GSM signalen kan ha en positiv effekt på utvecklingen av Alzheimer, men studien måste upprepas på större material och med annan design innan slutsatser kan dras.

I tidigare SSM rapporter dras slutsatsen att RF-exponering inte initierar tumörutveckling, dvs RF-exponering ensamt har ingen carcinogen effekt. Men i några tidigare studier har man sett att RF-exponering förstärker utvecklingen av tumörer som initierats med andra exponeringar. En ny studie har sett detta också vid exponering för en signal av den typ som förekommer vid 3G basstationer, med exponering över den vanliga nivån vid basstationer men under gällande gränsvärden. Utan bekräftelse från fler studier och från studier på andra djurslag går det inte att avgöra om detta är en reell effekt.

En flergenerationsstudie av effekter från en 3G basstationssignal på utvecklingen hos råtta visade inte några effekter. Samma resultat erhölls när två mobiltelefonsignaler undersöktes. De resultaten stämmer med tidigare slutsatser om att det inte verkar finnas några icke-termiska RF-effekter på utveckling.

Ett flertal studier kunde inte utvärderas beroende på bristande design och ofta saknades information om exponeringen. Precis som vid ELF så måste djurstudierna designas bättre för att kunna bidra till hälsoriskbedömningen.

Laboratoriestudier på försökspersoner

Ett antal högkvalitativa studier på EMF och sömnkvalitet och sömn-EEG har publicerats under det senaste året och de bidrar till att förstå en del motstridiga data som publicerats tidigare. EEG studierna visar återigen effekter av GSM (dvs pulsad signal) på alfa-bandet, medan motsvarande icke-pulsade signal inte visade några sådana effekter. Detta resultat bör studeras ytterligare bland annat i djurmodeller och på nervvävnad i in vitro-studier för att se hur den elektriska aktiviteten hos neuronala nätverk påverkas av GSM- och 3G-signaler (pulsade och icke-pulsade). PET-studier (imaging) har visat lovande resultat, men delvis motstridiga eventuellt beroende på skillnader mellan GSM och 3G signalerna.
Det finns nya neurovetenskapliga metoder (t ex brain imaging och brain stimulation) som skulle kunna användas för att undersöka ”elöverkänslighet”. Studier av effekter vid långtidsexponering och studier av effekter på barn saknas fortfarande.

Epidemiologiska studier

Möjligheten att mobiltelefonanvändning upp till omkring tio år skulle kunna påverka risken för hjärntumör kan uteslutas med betydande säkerhet baserat på resultaten i den nyutkomna slutrapporten från Interphone-studien och baserat på rapporter från cancerregister där hjärntumörsjukligheten kan följas över tid. Om mobiltelefonanvändning skulle öka risken för hjärntumör med 50% eller mer skulle hjärntumörsjukligheten i befolkningen gått upp med minst 30% sedan mobiltelefonin introducerades, om man antar en 60% användning i befolkningen. En sådan ökning skulle ha varit klart synlig i cancerstatistiken, om inte en lika stark skyddande faktor introducerats samtidigt. Vissa studier har till och med presenterat riskökningar på 100% eller mer vilket skulle varit ändå mer synligt i cancerstatistiken. Däremot skulle en risk för en lite undergrupp av hjärntumör kunna vara svårare att upptäcka på grund av mindre antal. Det är också svårare, och möjligen fortfarande för tidigt, att upptäcka långtidseffekter, säg effekter som tar 20 år att utveckla.
Två undersökningar av exponering från radio/TV-master med förhållandevis goda exponeringsdata publicerades 2009. De har nu följts upp av en första full-skalig undersökning

baserad på basstationer och som undersökte cancer hos barn. Det fanns inga samband mellan exponering för RF från basstationerna och sjukdomsrisk i den undersökningen. Man kan inte med säkerhet utesluta att det finns ett samband mellan exponering från sändare eller basstationer och barncancer utifrån denna och tidigare undersökningar, men tills vidare finns det inga resultat som tyder på att ett sådant samband skulle finnas.

Introduction

Preamble

In this preamble we explain the principles and methods that the IEG uses to achieve its goals.

Relevant research for EMF health risk assessment can be divided into broad sectors such as epidemiologic studies, experimental studies in humans, experimental studies in animals, and *in-vitro* studies. Also studies on biophysical mechanisms, dosimetry, and exposure assessment are considered.

A health risk assessment evaluates the evidence within each of these sectors and then weighs together the evidence across the sectors to a combined assessment. This combined assessment should address the question of whether or not a hazard exists i.e., if there exists a causal relation between exposure and some adverse health effect. The answer to this question is not necessarily a definitive yes or no, but may express the weight of evidence for the existence of a hazard. If such a hazard is judged to be present, the risk assessment should also address the magnitude of the effect and the shape of the dose-response function, i.e., the magnitude of the risk for various exposure levels and exposure patterns. A full risk assessment also includes exposure characterization in the population and estimates of the impact of exposure on burden of disease.

Epidemiological and experimental studies are subject to similar treatment in the evaluation process. As a general rule, only articles that are published, or accepted to be published, in English language peer-reviewed scientific journals are considered by the IEG. This does not imply that the IEG considers all published articles equally valid and relevant for health risk assessment. On the contrary, a main task of the IEG is to evaluate and assess these articles and the scientific weight that is to be given to each of them. The IEG examines all studies that are of potential relevance for its evaluations. However, in the first screening some of the studies are sorted out either because the scope is not relevant to the focus of a particular annual report, or because the scientific quality is insufficient to merit consideration. Such studies are normally not commented upon in the annual IEG reports. The IEG considers it to be of equal importance to evaluate positive and negative studies, i.e., studies indicating that EMF has an effect and studies not indicating the existence of such an effect. In the case of positive studies the evaluation focuses on alternatives to causation as explanation to the positive result: With what degree of certainty can one rule out the possibility that the observed positive result is produced by bias, e.g. confounding or selection bias, or chance. In the case of negative studies one assesses the certainty with which it can be ruled out that the lack of an observed effect is the result of (masking) bias, e.g., because of too small exposure contrasts or too crude exposure measurements; one also has to evaluate the possibility that the lack of an observed effect is the result of chance, a possibility that is a particular problem in small studies with low statistical power. Obviously, the presence or absence of statistical significance is only a minor factor in this evaluation. Rather, the evaluation considers a number of characteristics of the study. Some of these characteristics are rather general, such as study size, assessment of participation rate, level of exposure, and quality of exposure assessment. Particularly important aspects are the observed strength of association and the internal consistency of the results including aspects such as dose response relation. Other characteristics are specific to the study in question and may involve dosimetry, method for assessment of biological or health endpoint, the relevance of any experimental biological model used etc. For a further discussion of aspects of study quality, refer for example to the

Preamble to the IARC (International Agency for Research on Cancer) Monograph Series (IARC, 2002). It is worth noting that the result of this process is not an assessment that a specific study is unequivocally negative or positive or whether it is accepted or rejected. Rather, the assessment will result in a weight that is given to the findings of a study.

The step that follows the evaluation of the individual studies within a sector of research is the assessment of the overall evidence from that sector with respect to a given outcome. This implies integrating the results from all relevant individual studies into a total assessment. This is based on the evaluations of the individual studies and takes into account, for each study, both the observed magnitude of the effect and the quality of the study. Note again, that for this process to be valid, all studies must be considered equally irrespective of their outcome. In the experience of the IEG, tabulation of studies with results and critical characteristics has proven to be a valuable tool.

In the final overall evaluation phase, the available evidence is integrated over various sectors of research. This phase involves combining the existing relevant pieces of evidence on a particular end-point from studies in humans, from animal models, *in-vitro* studies, and from other relevant areas. The integration of the separate lines of evidence should take place as the last, overall evaluation stage, after the critical assessment of all (relevant) available studies for particular end-points. In the first phase, epidemiological studies should be critically evaluated for quality irrespective of the putative mechanisms of biological action of a given exposure. In the final integrative stage of evaluation, however, the plausibility of the observed or hypothetical mechanism(s) of action and the evidence for that mechanism(s) is a factor to be considered. The overall result of the integrative phase of evaluation, combining the degree of evidence from across epidemiology, animal studies, *in vitro* and other data depends on how much weight is given on each line of evidence from different categories. Human epidemiology is, by definition, an essential and primordial source of evidence since it deals with real-life exposures under realistic conditions in the species of interest. The epidemiological data are, therefore, given the greatest weight in the overall evaluation stage.

An example demonstrating some of the difficulties of making an overall evaluation is the evaluation of ELF magnetic fields and their possible causal association with childhood leukaemia. It is widely agreed that while epidemiology consistently demonstrates an association between ELF magnetic fields and increased occurrence of childhood leukaemia, the little support from observations in experimental models and the lack of support for plausible biophysical mechanisms of action leads to the overall evaluation of ELF magnetic fields, in IARC's terminology, as 'possibly carcinogenic to humans' (Group 2B).

Extremely Low Frequency (ELF) fields

New biological (experimental) studies

Cell studies

Cell redox state

It has been suggested that ELF magnetic field exposure affect oxidative stress and intracellular calcium ion (Ca^{2+}) homeostasis, which are two interrelated cellular processes in specific cell models. An Italian group has thus investigated the effects of ELF exposure (30 min, 0.1 and 1 mT) on the differentiation and function of muscle cell using the C2C12 cell line (Morabito et al., 2010). They found that exposure induced production of reactive oxygen species (ROS) in myoblasts and myotubes and a decrease in mitochondrial membrane potential; increased the activity of catalase and glutathione peroxidase which protects against ROS; and altered the homeostasis of Ca^{2+}. The data suggest a modification of the cell redox state caused by ELF exposure. If confirmed, other processes involving ROS and Ca^{2+}, which act as second messengers, may also be affected.

DNA

There have been a few reports describing the effects of ELF magnetic field exposure on DNA integrity in human cells, based on the Comet assay, e.g., (Ivancsits et al., 2005), followed by some controversies about the lack of reproducibility and the absence of a plausible scientific mechanism for these findings. A replication of the original experiment was thus performed in Switzerland in an attempt to assess the existence and cause of the effect (Focke et al., 2010). Intermittent (5 min ON, 10 min OFF) but not continuous 15-hour exposure (50 Hz, 1 mT) induced a small but significant increase in DNA fragmentation in human primary fibroblasts. The amplitude of the effect depended on cell proliferation, suggesting DNA replication rather than direct damage may have been affected. The authors concluded that the effects induced by ELF exposure might be rationalized in terms of minor disturbances in S-phase processes and occasional triggering of apoptosis rather than by DNA damage. There is still a need for confirmation of the existence of these effects.

Proliferation and differentiation

In a study performed in Bologna (Marcantonio et al., 2010), the effects of ELF magnetic fields (50 Hz, 1 mT) were tested on the proliferation and differentiation of the human neuroblastoma cell line BE2-C, representative of high-risk neuroblastomas. Cells were exposed for 24-72 h in the presence or absence of all-trans-retinoic acid, a neuronal differentiating agent. In the presence of EMF and retinoic acid, there was a decrease in cellular proliferation and alteration in the cell cycle. Moreover, there were alterations of morphological traits (number of neurites/cell, neurite length), and an increase in mRNA levels of p21(WAF1/CIP1) and cdk5 genes, involved in neuronal differentiation. The expression of the cyp19 gene, involved in neuronal differentiation and stress response was enhanced by retinoic acid treatment and enhanced further by magnetic field exposure. This is an example of effects of combined exposure to MF and a chemical agent.

Conclusion on ELF cell studies

Many new findings have been published in the last years on ELF magnetic field bioeffects. Most of the *in-vitro* studies are dealing with DNA damage, production of ROS and expression

of genes. They are mostly uncorrelated in terms of cell models and endpoints and performed under high-level exposure, i.e., in the mT range. Moreover, most of the *in-vitro* studies are not addressing directly the main issue, which are mechanistic explanations for the association between ELF exposure and childhood leukaemia.
The conclusion on genotoxic effects is that the differences between ELF-exposed and sham exposed cells have been small with little biological relevance (although statistically significant in some studies) with very few exceptions. As stated above, the current interpretation of the positive results does not imply that there is direct damage caused by ELF exposure and the health risk assessment must be done accordingly. Moreover, the trend is toward more studies performed with combined exposure to ELF magnetic fields and chemical or physical agents. This may help resolve the current uncertainty about the causality of the link between ELF exposure and childhood leukaemia.

Animal studies

ALS

Amyotrophic lateral sclerosis (ALS) has been linked to ELF exposure in several occupational epidemiological studies. In a pilot study, Poulletier de Gannes and co-workers used a transgenic mouse model that develops ALS to study the influence of long-term ELF exposure (Poulletier de Gannes et al., 2009). Groups of 7 mice were exposed to 100 µT or 1000 µT ELF magnetic fields or sham exposed for 2 h per day, 5 days per week and 7 weeks. Clinical signs of ALS begin to appear in this mouse strain at an age of approximately 16 weeks, which is in the 6th week of exposure. Body weight and life span were monitored and motor performance tested weekly before, during, and after exposure. Neither of the two exposure levels had any influence on any of the parameters assessed. Despite the limitations of this pilot study –with small numbers of animals – it provides no support for a causal association between ELF exposure and the development of ALS.

Cancer

The association that has been observed in epidemiological studies between childhood leukaemia and exposure to ELF magnetic fields is still unexplained. No indications have been obtained from experimental studies of a causal relationship. These studies have been hampered, however, by the lack of an adequate animal model for childhood leukaemia. A rat leukaemia model has recently been developed and was used by Bernard and colleagues to study the effects of long-term exposure to 50 Hz magnetic fields (Bernard et al., 2008). In this rat model, acute lymphoblastic leukaemia (which is the most common type of childhood leukaemia) is induced by n-butylnitrosourea (BNU). The animals were given BNU daily in the drinking water, for 5 days per week and 24 weeks, starting at an age of three months. Groups of 20 male rats were exposed to 100 µT sinusoidal 50 Hz magnetic fields with or without harmonics, for 18 h per day and 7 days per week. Harmonics were 150, 250 and 350 Hz, with intensities of 5, 6 and 5 µT, respectively. Exposure started simultaneously with BNU administration and continued for 52 weeks, upon which the surviving animals were sacrificed. Controls groups received BNU only (n=20) or no treatment (n=10). Four replicate experiments were performed. Also a positive control experiment was conducted, by exposing a group of 40 animals to 4.8 Gy gamma irradiation 12 days before the start of BNU treatment, with a control group of BNU only (n=40). Several parameters indicative of leukaemia were assessed regularly, and body weight and survival were monitored. None of the ELF exposure treatments had an influence on any of the parameters assessed. Therefore this study does not support the existence of a causal relation between ELF magnetic field exposure and childhood leukaemia. It should be noted that the animals used in this study were adults, so strictly

speaking not relevant for childhood leukaemia. Another problem was the high incidence of leukaemia in this model in the BNU-only control groups, up to 70%, which makes it difficult to detect relatively small stimulating effects of the physical agents used.

Chung et al (2010) investigated the influence of exposure to circularly polarized 60 Hz magnetic fields on the development of lymphoma in a strain of mice with a high incidence of this disease (Chung et al., 2010). Groups of 40 animals were exposed to 0 µT (sham controls), 5, 83.3 or 500 µT for 21 h per day for 40 weeks. None of the exposures had any influence on survival time, body weight, haematological and genotoxicity parameters, and necropsy findings. Upon termination of the experiment, the percentages of lymphoma in the four groups were not significantly different and varied between 75 and 80%. This study therefore suffers from the same problem as the previous one, in that the high incidence in the control group makes it difficult to detect any effect of exposure.

In an earlier study, the same authors (Chung et al., 2008) studied the influence of a circularly-polarized 60 Hz magnetic field on the development of brain tumours induced by N-ethyl-N-nitrosourea (ENU). In this study, groups of 28-38 animals were exposed to 0 (sham controls), 5, 83.3 or 500 µT for 21 h per day for 28 or 38 weeks. Body weight, haematological parameters, and expression of the *h-ras* gene were regularly performed, while survival was registered and necropsy performed. The incidence of brain tumours in the ENU-only controls was up to 57%, so effects of exposure would have been detectable. However, no effect of ELF exposure was seen on any of the investigated endpoints.

Jiménez-García et al (2010) investigated the effect of exposure to a 4.5 mT 120 Hz magnetic field on the development of chemically-induced preneoplastic lesions in the rat liver (Jimenez-Garcia et al., 2010). Groups of 6 rats were exposed or sham exposed for 50 min per day from 7 days before the start of chemical induction up to 25 days after, and were then sacrificed. Another group of 6 animals served as untreated controls. The effects of exposure on liver carcinogenesis, apoptosis, proliferation and cell cycle progression were evaluated by histochemical, TUNEL assay, caspase 3 levels, immunohistochemical and western blot analyses. It was concluded that the exposure had an inhibitory effect on the development of preneoplastic lesions through a reduction of cell proliferation, but without altering apoptosis. The small group size makes it difficult, however, to draw firm conclusions whether this is a promising therapeutic approach.

Conclusion on ELF animal studies

The question of whether ELF magnetic fields have any influence on the development of ALL in children still remains unresolved. Although a rat ALL model has been developed, it was only applied in adult animals. Moreover, only small groups were used, which makes it virtually impossible to perform any proper statistical analyses. This has been a problem in several of the studies described. Another problem is the high incidence of disease in control groups, which hampers detection of relatively small effects. Animal studies have to use better designs in order to be useful for health risk analysis. However, new investigations are underway or planned that should provide more information in the next years.

New epidemiological studies

CANCER

Residential exposure and childhood cancer

A small Japanese case-control study was conducted including 55 childhood brain tumours and 99 controls (Saito et al., 2010). The cases were aged 0-14 years and recruited from 107 hospitals. A third of the eligible cases participated. The controls were recruited through resident registers with matching on age, sex and region and participation proportion was 27%. Extensive one-week EMF measurements using the Emdex Lite dosimeter were carried out in the subjects' bedrooms and additional spot measurements were performed in other rooms. The average time between diagnosis and measurements was 1.1 year.
An elevated risk of brain tumours was associated with bedroom EMF of 0.4 μT or higher (OR=10.9, 95% CI 1.05-113) based on three exposed cases and one exposed control. A non-significantly increased OR was found also for 0.2-0.4 μT (OR=1.6, 95% CI 0.3-9.8, two cases and four controls). Adjustment for potential confounders had no strong impact on point estimates but introducing other covariates than maternal education rendered the findings for EMF non-significant.
The study had a good exposure measurement procedure, but was strongly limited by the small sample size. Also, low participation is a concern.

A case-control study of childhood cancer in relation to residential exposure to ELF magnetic fields from power lines during the first year of life was conducted in the UK (Kroll et al., 2010). The cases were identified from the National Registry of Childhood Tumours, born in 1962-1995 and diagnosed during the same period at age below 15 years. One control per case was selected from the Office of National Statistics. ELF-EMF magnetic field exposure during the year of birth was calculated based on distance to the power line as well as voltage, current and phasing. Detailed information was sought for the 1% of the subjects living within 200 or 400 m of the power line, depending on the characteristics. Missing residential coordinates or power line data led to exclusion of 12% of the subjects from the analysis.
Only eight cases and five controls had calculated magnetic field strengths of 0.4 μT or higher, and the numbers with 0.2-0.4 μT were even smaller. The odds ratio for such exposure relative to <0.2 μT was 2.0 (95% CI 0.2-22) for leukaemia and 0.3 (95% CI 0.0-3.2) for nervous system tumours.
The findings are consistent with results of previous studies, but also with null results, and do not add much to the precision of the overall assessment. The study population overlapped with the previous UKCCS study, but the exposure assessment was focused differently (though using similar methods for calculation of field strength). The main limitation was the small number of exposed cases, but also the lack of power line characteristics for a quarter of the potentially high-exposure residences is a concern.

A meta-analysis of published results of residential ELF magnetic field exposure and childhood brain tumours included 13 studies with more than 8800 cases (12 case-control studies and one cohort study) (Mezei et al., 2008). Five studies addressing distance from power lines gave a pooled OR=0.88 (95% CI 0.6-1.4) for distances <50 m. Four studies with calculated fields showed pooled OR=1.13 (0.7-2.0). Three studies using spot measurements provided a pooled OR=1.13 (95% CI 0.6-2.1), but inclusion of an early Swedish study with residences as units increased it to 1.5 (95% CI 0.9-2.6). The four studies with long-term measurements (from 24 hours to one week) showed a combined OR=1.14 (95% CI 0.7-2.0). Five studies with calculated or measured field gave a pooled OR=1.68 (95% CI 0.8-3.4) for

>0.3 or >0.4 μT (19 exposed cases). There was little evidence of publication bias. Heterogeneity between studies was found only for wire-code studies (pooled OR=0.83; 95% CI 0.5-1.4). The meta-analysis did not provide strong support for an association between ELF magnetic fields and childhood brain tumours. The findings were more firmly negative compared with the previous meta-analyses performed more than 10 years earlier.

A pooled analysis combined original data from nine studies on residential ELF exposure and childhood brain tumours (Kheifets et al., 2010b). Exposure assessment was based on measurements of calculated field strengths. A total of 8371 cases were included in the analysis. The pooled estimate for fields ≥0.4 μT was OR=1.14 (95% CI 0.61-2.13) and there was no indication of a monotonous exposure-effect relation. The results showed no significant heterogeneity between studies. The findings of the meta-analysis reconfirm the earlier results and add to consistency of the evidence, but otherwise offer little new guidance to the interpretation of the deadlock between epidemiology and other lines of evidence regarding cancer risk from ELF.

Kheifets and collaborators conducted a pooled analysis of seven studies of childhood leukaemia published after 2000 involving more than 10,000 cases and nearly 13,000 controls aged 0-15 years (Kheifets et al., 2010a). All were matched population-based studies (three hospital-based studies were excluded) and used either measured or calculated field strengths. There was no significant heterogeneity between the studies. The pooled odds ratio for ≥0.3 μT was 1.44 (95% CI 0.88-2.36, based on 26 exposed cases), which, despite the wide confidence interval, is consistent with the earlier meta-analyses. The pooled result for ≥0.4 μT was similar to those in previous meta-analyses if the Brazilian study was omitted (OR=2.02; 95% CI 0.87-4.69), since several unique features of the Brazilian study raised questions about the potential for bias in that study. Both linear and non-parametric analyses gave results that were consistent with an exposure-response pattern. Also, residence within 50 m of a power line was associated with an increased risk (OR=1.59; 95% CI 1.02-2.50).

Parental EMF exposure and childhood cancer

A large German case-control study evaluated the relation of parental occupational ELF-EMF exposure and risk of childhood cancer (Hug et al., 2010). The material was based on two previous studies and consisted of 846 leukaemia, 444 brain tumour, and 759 other cancer cases diagnosed before age 15 in West Germany identified from the nationwide childhood cancer registry with 95% completeness. The controls were recruited through resident registers with matching on gender, age and region. Participation proportion was 82% for cases and 71% for controls. Occupational histories of parents were assessed by means of self-administered questionnaires supplemented by telephone interviews. A job-exposure matrix based on expert opinion and spot measurements (numbers and selection criteria not specified) was used to classify exposures.

Approximately 24% of the fathers of the cases and controls were classified as exposed to ELF magnetic fields with flux density exceeding 0.2 μT. Neither leukaemias, brain tumours, nor other malignancies were associated with father's occupational exposure. The primary analysis dealt with exposure levels above versus below 0.2 μT and the OR's for the higher exposure levels were close to unity for all tumour types. In a secondary analysis with additional cut-points at 0.1 and 1 μT little evidence for increased risks was found, though an OR of 1.19 (95% CI 0.8-1.8) was obtained for central nervous system tumours with >1 μT. Maternal exposures were infrequent (6% above 0.2 μT) and results did not indicate increased risks (OR=0.9 for leukaemia and brain tumours with exposure >2 μT). Adjustment for potential confounders did not affect the findings.

This is a very large study and its main limitation is the crude information on EMF exposure and the rare maternal exposure. Though the results are reassuring, non-differential misclassification may dilute possible associations.

A Canadian study assessed maternal occupational EMF exposure in relation to childhood brain tumour (Li et al., 2009). The material was combined from previous Québec and Ontario studies. Both enrolled cases aged below 15 years from hospitals and used various population registers for identifying controls. Maternal occupation history was assessed by telephone interviews. The overall participation among cases was roughly 87% and among controls slightly below 80%. A job-exposure matrix was constructed for the Québec study by an expert and was also applied for the Ontario study. The matrix was not applicable to a fifth of the jobs.
A total of 548 cases and 760 controls were included in the analysis. In the pooled results, median cumulative and average exposures were similar for cases and controls before conception and during pregnancy. For the two-year period preceding the pregnancy, a slightly increased risk was found for average exposure 0.3 μT or above (OR=1.4; 95% CI 1.0-2.1 based on 69 exposed cases). Similarly, an elevated OR was found for the highest decile of average exposure during pregnancy (OR=1.5; 95% CI 1.1-2.2 based on 63 exposed cases). For cumulative exposure, non-significantly increased results were obtained both prior to and during pregnancy (OR=1.3-1.4). When analysed by histological type, a significantly increased risk related to average exposure during and before pregnancy was observed only for astroglial tumours, with similar though non-significant result for other glial tumours, but no indication of risk for primitive neuroectodermal tumours.
The consistency of the findings and the comparability of the exposure assessment methods between the two studies is a concern. The positive results were mainly based on the Ontario data, though the method was developed for the Québec study and its validity is likely to be better in that material. The participation was relatively high, reducing the likelihood of selection bias.
The research findings are not very consistent, as previous studies have shown little indication of increased risk. Firm conclusions are difficult to draw but there appears to be little support for the hypothesis relating parental exposure to cancer risk in the offspring.

Adult cancer

Risk of brain tumours in relation to occupational EMF exposure was evaluated in a hospital-based case-control study in the US (Coble et al., 2009). The cases were 489 adults diagnosed with glioma and 197 with meningioma identified from three hospitals. The 799 controls were selected from patients seen in the same hospitals with other conditions than cancer. Participation rates were not reported. Computer-assisted personal interviews were carried out to elicit occupational histories including job titles, industry, tasks and in particular use of electronic tools or equipment. In addition to a previously developed job-exposure matrix, a job-specific module was constructed to classify intensity (distance from the source) and duration of exposure (work hours with electronically powered equipment). Cumulative exposure (μT years), life-time average exposure and maximum exposure as well as duration of work with exposure exceeding 0.15 μT were analysed and none of the indicators showed increased risks for all gliomas or glioblastoma as a separate group, or for meningioma. All point estimates were close to unity with upper confidence limits ranging 1.1-1.8 for various tumour types and exposure indices.
The strengths of the study include the relatively large size (mainly for gliomas). Exposure assessment was based on detailed interview, but lacked any direct measurements (which

would require reconstruction of past circumstances for a case-control study). The internal consistency of the results is reassuring.

In the German Interphone study, associations of occupation with the risk of intracranial tumours were assessed (Samkange-Zeeb et al., 2010). The cases (366 gliomas, 381 meningiomas and 97 schwannomas) were identified from four neurosurgery clinics and controls drawn from population registry. Occupational history was constructed based on standard classification of job titles obtained in personal interview. Six occupational sectors were defined, one of which was "electrical". Few elevated risk were found, no significant associations with any branch of industry for glioma or meningioma. For acoustic neuroma, employment for five years or more in the electrical industry was associated with an increased risk (OR=3.39; 95% CI 1.03-11.10).

A meta-analysis was recently published on ELF magnetic fields and breast cancer (Chen et al., 2010). The rationale was to evaluate evidence that has emerged after a previous meta-analysis, which showed no evidence of risk in 2000. The current analysis covered 15 studies published in 2000-2009, with more than 24,000 cases and 60,000 controls. A systematic literature search was performed for population-based case-control studies on breast cancer and electromagnetic fields published in English. Ten studies used field strength measurements (generally with a cut-off of 0.2 μT). Random effects model was used in the analysis except for electric blankets. No increased risks were found for occupational or residential EMF exposure (nor for electric blankets specifically based on five studies). The upper confidence limits were close to 1.1. Sub-group analyses by oestrogen-receptor and menopausal status gave also consistent results.
This paper reconfirms lack of association between ELF magnetic field exposure and breast cancer risk. Further studies appear difficult to justify.

OTHER DISEASES

Alzheimer's disease

A cohort study with the entire Swiss population aged 30 years or older evaluated the relationship between residential proximity to power lines and death from neurodegenerative diseases (Huss et al., 2009). Information on residential coordinates was obtained from the census of 2000 and for institutionalised subjects from 1990 census (1% with missing coordinates). Coordinates for 220-380 kV power lines were received from a federal authority. Causes of death in death certificates were linked to census data using deterministic and probabilistic techniques with 95% success. Follow-up covered years 2000-2005 and there were more than 9000 deaths from Alzheimer's disease, 28,000 from unspecified senile dementia, nearly 6700 from Parkinson's disease, 744 from amyotrophic lateral sclerosis (ALS), and 773 from multiple sclerosis (MS). People living within 50 m of power lines for at least 10 years (compared with ≥600 m) had an increased mortality from Alzheimer's disease (Hazard Ratio (HR)=1.78; 95% CI 1.07-2.96). The risk was related to the duration of residence in the 50 m corridor. The results were similar for men and women and persons aged below or above 85 years. Somewhat lower risks were seen for senile dementia and no association with deaths from Parkinson's disease, MS or ALS. Overall mortality or deaths from liver disease or lung cancer were evaluated as indicators of socioeconomic status and lifestyle related health behavior, and they were not increased in the proximity to power lines.

Work-related exposure to extremely low-frequency magnetic fields and dementia was investigated in a population-based cohort study of Swedish twins (Andel et al., 2010). For

members of the Swedish Twin Registry who were at least 65 years of age, information about occupation was collected by means of a telephone interview in 1998. Subsequently, a random sample was selected each month for a cognitive dysfunction screening by phone interview. Positive cognitive dysfunction screening was followed by an in-person clinical diagnostic evaluation for dementia. Eventually 216 individuals were classified as dementia cases (141 with Alzheimer's disease) and 9,292 participants were included as controls in the analyses (47% of all eligible twins). In tendency, dementia and AD were associated with EMF exposure, although not significant (e.g. OR for dementia in occupations with ≥0.2 μT compared to low exposure occupations (<0.12 μT): 1.38; 95%-CI 0.93-2.03). In stratified analyses stronger associations were found for participants with disease onset before the age of 75 (for dementia ≥0.2μT vs. <0.12: OR=2.01 (95% CI: 1.10-3.65), for men OR=1.81 (95% CI 0.84-3.88) and for manual workers OR= 1.75 (95% CI: 1.00-3.05). Notably, the point effect estimates were considerably higher when considering only 42 twin pairs discordant for dementia (OR=3.0; 95% CI: 0.8-11.4) or 22 twin pairs discordant for AD (OR=7.1; 95% CI: 0.6-82). These latter findings are, however, hampered by the small sample size. Prospective collection of exposure data and clinically verified diagnoses are strength of this study. On the other hand, for 251 dementia cases exposure information could not be obtained as a result of illness and absence of an informed proxy, which may have introduced a bias. As the study involves analysis of prevalent dementia cases, differential survival rates could create a confounding.

A meta-analysis of occupational EMF exposure and risk of Alzheimer's disease covered nine case-control and five cohort studies published in 1995-2004 (Garcia et al., 2008). Papers published in languages other than English or Spanish were excluded. Random effect model and meta-regression analysis was used. Of the total of more than 5000 cases, half (54%) were from case-control studies. Pooled results from all case-control (OR=2.0; 95% CI 1.4-3.0) and all cohort studies (RR=1.6; 95% CI 1.2-2.3) showed increased risk but also substantial heterogeneity in results. A significantly increased risk was found for men in cohort studies (pooled RR=2.1; 95% CI 1.5-2.8) and women in case-control studies (pooled OR=3.9; 95% CI 1.9-8.2) (the gender difference was however significant only for cohort studies). Case-control studies with Alzheimer's diagnosis based on clinical examination showed more evidence for increased risk than those using death certificates, while the reverse was true for cohort studies (though the difference between criteria was significant only for case-control studies). Exposure intensity (estimated magnetic flux density) was related to risk of Alzheimer's disease for the cut-off of 0.2 μT for case-control studies (but not 0.3 μT) and 0.5 μT for cohort studies (but not 0.2/0.3 or 1.0 μT). No significant exposure-effect relation was found. There was evidence for publication bias (larger effect sizes in smaller studies), particularly for case-control studies.
The findings warrant further investigation of the topic. However, heterogeneity between studies indicates lack of consistency and there was no monotonic dose-response. Further, publication bias may exaggerate the effect size. The relation of the case definition (deaths from Alzheimer's disease versus incident cases) to the results differed between case-control and cohort studies (the former showing higher and the latter lower risk for studies using clinical examination). This is an area of priority for future studies, primarily those with high-quality diagnoses.

Current overall conclusion on epidemiology

For ELF magnetic fields and risk of childhood leukaemia, previous conclusions still hold: a consistent association has been observed, but a causal relationship has not been established. Evidence regarding breast cancer weighs against an increased risk. Little new information has

become available concerning parental exposure and risk of childhood cancer. Some evidence for a possible association of Alzheimer's disease with ELF magnetic field exposure has been obtained and further research is warranted.

Radiofrequency (RF) fields

New biological (experimental) studies

Cell studies

Mechanisms

The hypothesis that living cells can demodulate RF carriers was tested in a joint investigation in the USA and UK, using a doubly resonant cavity (Kowalczuk et al., 2010). Cell and tissue samples were exposed to continuous wave (CW) RF at the resonant frequency of the cavity (ca. 900 MHz) at 0.1 or 1 mW, and monitored for the generation of the second harmonic. The samples were cell suspensions, adherent cells and thin sections or slices of mouse tissues (e.g., brain, kidney, muscle), either viable or non-viable. No second harmonic of the incident signal was detected, in spite of the very low noise level (–169 dBm). Since such generation of harmonics is a necessary and sufficient condition for evidence of demodulation, these negative results do not support the hypothesis that living cells can demodulate RF energy.
In terms of mechanistic hypotheses heating remains the only known mechanism of interaction of RF with living tissues. However, evidence of effects on EEG (see below), if confirmed, might lead to reconsideration of his conclusion.

Genotoxic outcomes – DNA damage and reactive oxygen species (ROS)

There is still a lot of controversy regarding the data of the Rüdiger group in Vienna about their publication on DNA damage in rat and human cells after exposure to GSM signals (Diem et al., 2005). Several critical comments (Vijayalaxmi et al., 2006) and answers were published (Rüdiger et al., 2006). Lerchl and Wilhelm (2010) recently described their own statistical analysis of the data (Lerchl and Wilhelm, 2010). These authors conclude that the (Diem et al., 2005) publication should be retracted. The answer by (Rudiger and Adlkofer, 2010) contradicts all of the arguments of Lerchl and Wilhelm and gives as evidence of effects two of the papers described below (Franzellitti et al., 2010; Xu et al., 2010). No firm conclusion can thus be drawn today, but the positive results of the Vienna group are not in line with other publications, in some contrast with those in the ELF range (see above).

An Italian group had reported that a 1-hour exposure to a GSM-1800 signal at 2 W/kg did not cause increased levels of primary DNA damage in HTR-8/SVneo human trophoblast cells (Valbonesi et al., 2008). In a further investigation by the same group, the same cells were exposed for 4, 16, or 24 hours to various GSM-1800 signals (GSM-217 Hz and GSM-Talk with intermittent exposure: 5 min field ON, 10 min field OFF) and continuous wave at 1800 MHz (Franzellitti et al., 2010). The alkaline comet assay was used to evaluate primary DNA damage and/or strand breaks due to uncompleted repair processes. The GSM signals induced a significant increase in DNA damage after 16- and 24-hour exposures, but CW RF were ineffective. However, the DNA integrity of the GSM-exposed cells was similar to that of sham-exposed cells within 2 hours of recovery. This suggests that the effect is indirect and has to do with DNA repair rather than DNA damage.

Using also the comet assay, a Chinese group investigated whether exposure to GSM-1800 at 2 W/kg altered DNA repair in human leukocytes exposed to X-rays (Zhijian et al., 2009). Leukocytes from four young healthy donors were exposed for 24 h (5 min ON, 10 min OFF), and then to X-rays at 0.25-2.0 Gy. DNA damage was at 0, 15, 45, 90, 150, and 240 min after exposure to X-rays. The DNA repair percentage served as the indicator of the DNA repair speed. There was inter-individual variability among donors in terms of DNA repair after X-ray exposure, but RF exposure did not induce DNA damage nor exhibited synergistic effects with X-rays.

The same Chinese group recently studied the effects of GSM-1800 signals at 2 W/kg on DNA repair in human B-cell lymphoblastoid cells exposed to doxorubicin (DOX[1]) at doses ranging between 0 and 0.2 µg/ml (Zhijian et al., 2010). DNA damage was detected up to 24 hours after exposure to DOX. RF exposure did not induce DNA damage, while DOX did as expected in a dose-dependent manner. RF exposure for 2 hours followed by simultaneous exposure to RF and DOX, or exposure to RF for 6-24 hours after exposure to DOX also induced DNA repair at 6 and 12 hours after exposure to DOX at concentrations above 0.075 µg/ml.

In France, the cytogenetic effects of GSM-900 signals were investigated using R-banded karyotyping[2] after exposure of human amniotic cells for 24 hours at 0.25 W/kg (Bourthoumieu et al., 2010). Genotoxic effects were assessed immediately or 24 h after exposure. There was no direct cytogenetic effect of GSM-900 exposure, either immediately or 24 hours after exposure.

As mitochondrial DNA (mtDNA) is particularly susceptible to oxidative stress, the purpose of a Chinese study was to determine whether RF exposure cause such damage to mtDNA (Xu et al., 2010). Primary cultured cortical neurons were exposed to a GSM-1800 signal at 2 W/kg. After 24 h of exposure, there was a significant increase in the levels of 8-hydroxyguanine (8-OHdG), a common biomarker of DNA oxidative, while the levels of mitochondrial RNA (mtRNA) transcripts decreased. These RF effects were reversed by pretreatment with the antioxidant melatonin. Together, these results suggested that exposure to GSM-1800 signals causes oxidative damage to mtDNA in primary cultured neurons.

A French study was carried out using for the first time the EDGE (2.5 G) signal[3] on three human brain cell lines: SH-SY5Y, U87, and CHME5, used as models of neurons, astrocytes, and microglia, respectively, as well as on primary cortical neuron cultures (Poulletier de Gannes et al., in press). A GSM-1800 exposure apparatus (IT'IS-Foundation, Zürich, Switzerland) was modified for *in-vitro* exposure to the EDGE signal at 2 and 10 W/kg for 1 and 24 hours. Production of ROS was assessed by flow cytometry using the dichlorofluorescein diacetate (DCFH-DA) probe at the end of a 24-hour exposure or 24 hours after a one-hour exposure. Exposure to the EDGE signal did not induce oxidative stress under these conditions, even at 10 W/kg. These results are in agreement with the earlier negative findings indicating that RF exposure alone does not lead to an increase in ROS production.

Genotoxic outcomes – Combined exposure

There is clearly a need for more investigations on effects of co-exposure to RF and chemicals.

[1] Antibiotic used for cancer treatment that induces DNA damage
[2] Visualization of the chromosomes using staining which allows visualizing all the chromosomal rearrangements, either numerical or structural,
[3] Enhanced Data on Global Evolution

A Finnish group (Luukkonen et al., 2010) investigated possible cooperative effects of RF and the catalyst ferrous chloride ($FeCl_2$) on ROS production and subsequent DNA damage. The fluorescent probe DCFH-DA was used to test intracellular ROS production as a possible underlying mechanism of DNA damage, which was quantified using the alkaline comet assay. Exposures were performed at 872 MHz and 5 W/kg using continuous waves (CW) or the GSM signal. Human neuroblastoma (SH-SY5Y) cells were exposed to RF and 10 µg/ml $FeCl_2$ for 1 hour. In the comet assay experiments, the exposure lasted 3 hours. As expected, treatment with $FeCl_2$ alone caused significant increase in ROS levels but there were no effects from either CW or modulated RF radiation on ROS production, DNA damage, or cell viability, or synergy with ferrous chloride.

Non genotoxic outcomes – Heat shock proteins (HSP)

There is a continuous drive for investigating the potential effects of RF exposure on the expression of heat shock proteins (Hsps) and in particular Hsp70 and Hsp27, which are known to be elevated in several human tumours.
A Chinese group exposed three human glioma cell lines to 1950 MHz CW RF for 1 hour at 1 and 10 W/kg (Ding et al., 2009). The localization and expression of Hsp27 and phosphorylated Hsp27 were examined by immunocytochemistry. RF exposure did not affect the distribution or expression of Hsp27. In addition, Western blotting showed no alteration in protein expression of Hsp27 or Hsp70 under all exposure conditions for the three cell lines. These results are in good agreement with previous data of the Roti Roti group (Vanderwaal et al., 2006).

Non genotoxic outcomes – Cell proliferation and gene expression

In Japan, the effects of RF exposure on cell proliferation and gene expression were investigated by (Sekijima et al., 2010) in human cell lines (glioblastoma, neuroglioma, and foetal lung fibroblasts). Cells were exposed to 2140 MHz CW and W-CDMA RF signals at 80, 250, or 800 mW/kg for up to 96 hours. There was no difference in cell growth or viability between exposed and sham-exposed groups. Very few (< 1%) genes (among 16,000-19,000) exhibited altered expression.

An Austrian group (Gerner et al., 2010) used a sensitive proteome analysis method to study changes in protein synthesis in cultured human cells lines and primary cells exposed at 2 W/kg to intermittent GSM-1800 signals (5 min ON and 10 min OFF). Autoradiography of 2D gel spots was used to measure increased synthesis of individual proteins. An 8-hour exposure caused a significant increase in protein synthesis in Jurkat T-cells and human fibroblasts, and to a lesser extent in activated primary human mononuclear cells (mainly chaperone proteins). Fourteen proteins were found to be specifically up-regulated and were subsequently identified by mass spectrometry. The authors interpret the results as evidence of a nonthermal mechanism based on RF-induced disturbances of hydrogen bonds, since most of the proteins induced by RF exposure were chaperones, mediators of protein folding. However, this mechanistic explanation is not plausible as there are no resonance absorptions of RF below ca. 150 GHz, but replication of these results obtained using a well-defined exposure system is warranted.

Non genotoxic outcomes – Microglial cells

The *in-vitro* activation of microglial cells was studied by a Japanese group under exposure to W-CDMA-2000 RF signals (Hirose et al., 2010). The exposure was carried out for 2 hours at 0.2, 0.8, and 2.0 W/kg. Functional changes in microglial cells were assessed by examining changes in the expression of immune reaction-related molecules and cytokine production, 24

and 72 h after exposure. The percentage of cells positive for major histocompatibility complex (MHC) class II was similar in exposed and sham groups. Moreover, the production of tumour necrosis factor-alpha, interleukin-1beta, and interleukin-6 (IL-6) were unaffected. The authors conclude that under those *in-vitro* exposure conditions, RF exposure at up to 2 W/kg does not activate microglial cells.

Non genotoxic outcomes – Calcium

There have been reports of effects of RF exposure on calcium ion (Ca^{2+}) homeostasis. In recent years, these studies have been few and negative, but one research group, expert in calcium homeostasis, has revisited the topic (O'Connor et al., 2010). They used a high-throughput imaging platform to monitor changes in cellular Ca^{2+} concentration in cells[4] exposed to GSM-900 signals or to CW fields at SAR ranging from 0.012 to 2 W/kg. There was no effect of RF exposure on either basal Ca^{2+} homeostasis or provoked Ca^{2+} signals[5]. The authors concluded that under their experimental conditions using a highly-sensitive assay, they could not detect any effect of GSM-900 exposure on Ca^{2+} homeostasis.

Fertility

Several recent studies have indicated that RF fields may have an adverse effect on human sperm quality, which might translate into an effect on fertility. A South African group had found no effects of GSM-900 exposure on mitochondrial membrane potential and motility of human spermatozoa (Falzone et al., 2008). They recently assessed the effects of similar exposures (1 hour, GSM-900 at 2.0 W/kg) on acrosome reaction,[6] evaluated by flow cytometry, which was not altered by RF exposure (Falzone et al., 2010a). The authors reported, however, that sperm morphology was altered: immediately or 1 h after exposure, the size of the spermatozoa and the relative proportion of the acrosome region were decreased compared to sham-exposed.

In another study by the same group, the effects of RF exposure on the induction of apoptosis-related properties in human spermatozoa were examined (Falzone et al., 2010b). Highly-motile human spermatozoa were exposed to GSM-900 at 2.0 and 5.7 W/kg. At various times after exposure, flow cytometry was used to examine caspase 3 activity, externalization of phosphatidylserine, induction of DNA strand breaks, and generation of ROS. Exposure had no effect on any of the parameters studied. According to the authors, this suggests that the impairment of fertility reported in some studies was not caused by the induction of apoptosis in spermatozoa.

The conclusion from these two studies by the same group is that few parameters are altered in spermatozoa under RF exposure even at high SAR level.

Conclusion on RF cell studies

The main endpoints investigated are DNA damage, production of ROS, expression of genes (HSP in particular) and effects on spermatozoa. No new non-thermal biological effect of RF exposure has been established. However, the number of ongoing studies on the effects of combined exposures (RF + chemical or physical agent) is increasing despite the current decrease in research funding.

[4] Human endothelial cells, PC-12 neuroblastoma and primary hippocampal neurons
[5] Using an InsP3-generating agonist and the Ca^{2+}ATPase inhibitor thapsigargin
[6] Shedding of the acrosome, which is an organelle that develops over the anterior half of the head in the spermatozoa

Animal studies

Nervous system

Several studies measured gene and protein expression in rodent brain in response to exposure to mobile phone signals. Ammari and colleagues (Ammari et al., 2010) exposed two groups of 6 rats to the signal of a 900 MHz mobile phone, for 45 min per day at a brain-average SAR level of 1.5 W/kg, and two groups for 15 min per day at a SAR level of 6 W/kg, for 5 days per week during 8 weeks. Control groups were sham exposed or untreated cage controls. One group of each exposure schedule was used to measure the expression of glial fibrillary acidic protein (GFAP) in various regions of the brain at 3 and at 10 days after the last exposure, respectively. GFAP is found in astrocytes, and an increased expression could indicate astrocyte activation, in response to brain damage. At both SAR levels and both assay times increased GFAP levels were observed, which would indicate an adverse effect of exposure on the brain.

Maskey et al (2010a) investigated the effect of exposure to a 835 MHz mobile phone signal on calcium binding proteins and apoptosis in the hippocampus of the mouse brain (Maskey et al., 2010b). They exposed a group of 10 mice at a SAR of 1.6 W/kg, for 8 h/d and 3 months. A decrease in calbindin activity and an increase in GFAP immunoreactivity were observed in the exposed group. The TUNEL (terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling) assay revealed apoptotic cells in several areas of the hippocampus in exposed animals only.

In a further study by this group (Maskey et al., 2010a), groups of 10 mice were exposed to the same 835 MHz signal at different exposure times and absorption rates: 1 h/day for 5 days at a SAR of 1.6 of 4.0 W/kg, 5 h/day for 1 day at a SAR of 1.6 or 4.0 W/kg, and daily exposure for 1 month at a SAR of 1.6 W/kg. The authors state that the exposure for 1 month resulted in almost complete loss of pyramidal cells in the CA1 area of the hippocampus, which can be indeed be seen on the photomicrographs presented. This is not corroborated, however, by the numerical analysis presented. This shows various effects, both increases and decreases of calcium binding proteins in various areas of the hippocampus, but no clear dose-related effect of exposure can be seen.

Finnie and co-workers studied other auxiliary cells in the brain, the microglia (Finnie et al., 2010). These cells are thought to respond rapidly to any change in their microenvironment. Groups of 10 mice were exposed to a 900 MHz signal at a whole body SAR of 4 W/kg for 60 min, or five successive days per week for 104 weeks. The exact exposure schedule for this long term arm of the study is not clear, however. Controls included sham and cage controls, and positive mechanical brain injury controls. Neither the acute nor the long term exposure resulted in an increased activation of microglia cells.

Kesari and Behari (2009) exposed 6 rats to 50 GHz fields, resulting in a SAR of 0.8 mW/kg, for 2 h per day and 45 days (Kesari and Behari, 2009). A second group of 6 rats was sham exposed. Immediately after the last exposure, animals were killed and whole brain homogenates were prepared. The level of protein kinase C (PKC), the number of DNA double-strand breaks, and the levels of the antioxidant enzymes superoxide dismutase, glutathione peroxidase and catalase, were determined. Several changes in enzyme levels as well as an increase in DNA double-strand breaks were observed in exposed animals. As with

the parallel study on sperm in these animals, the explanation for these observations is difficult, given the fact that the penetration of 50 GHz fields is only shallow: the authors consider it to be confined to the subcutaneous region.

These studies indicate that in rodents several weeks of daily exposure of 45 min or longer to a mobile telephone signal at a SAR of 1.5 W/kg and higher may result in a response in hippocampal neurons that indicates activation in response to injury. This might have an effect on memory and cognitive functions.

Several studies were published that unfortunately cannot be interpreted because of a lack of proper exposure data (Dasdag et al., 2009; Orendacova et al., 2009; Ragbetli et al., 2010; Ragbetli et al., 2009). Performing and publishing studies without such information is a waste of resources.

Behaviour, memory

Several studies have been performed into the effects of RF exposure on rodent behaviour and memory (Daniels et al., 2009; Kumar et al., 2009; Narayanan et al., 2010; Narayanan et al., 2009). However, because of a lack of proper dosimetry these studies cannot be interpreted.

Alzheimer's disease

A study that received a lot of attention was that of Arendash and colleagues on the effect of exposure to a mobile signal on development of Alzheimer's disease (Arendash et al., 2009). Groups of 6 mice of a transgenic strain exhibiting features similar to those of Alzheimer patients and of a non-transgenic strain were exposed to a 918 MHz mobile phone signal for 2x 1 h per day for up to 7 months, at a whole body SAR level of 0.25 W/kg. Studies with young adults started exposure at an age of 2-2.5 months and continued until 9.5 month of age. With aged adults exposure started at an age of 5 months and continued until 13.5 months of age. Similar groups of animals were sham exposed. During the exposure period, cognitive functions were regularly tested and at the end of the experiment the brains of the animals were studied for markers of Alzheimer's. In the young adult studies, the deterioration in cognitive performance seen in the untreated 'Alzheimer' group was not observed in the exposed group, where even an increase in performance was observed. Enhanced cognitive performance was also seen in the exposed 'non-Alzheimer' control group. In the exposed 'Alzheimer' group biochemical markers of Alzheimer's were decreased compared to the unexposed group, but no effect of exposure on oxidative stress was observed. In the exposed 'non-Alzheimer' control group oxidative stress was decreased in comparison to the unexposed group. In the aged adult studies, 'Alzheimer' mice exhibited cognitive impairment at the start of the exposure period, while the 'non-Alzheimer' controls did not. Testing at 2 and 5 months exposure did not reveal any effect, but at 8 months exposure cognitive function in the 'Alzheimer' mice was significantly better than in the unexposed animals. A similar albeit smaller effect was seen in the 'non-Alzheimer' control mice. As was the case with the young adults, biochemical markers of Alzheimer's were decreased in the exposed 'Alzheimer' group compared to the unexposed group. In the aged adults, core body temperature was measured at 8.5 months of exposure, both during and in between periods of exposure. In 'Alzheimer' as well as 'non-Alzheimer' mice the temperature was increased during exposure, although only significantly in the 'Alzheimer' group. In a separate experiment in untreated mice, body temperature was found not to change during exposure. The authors speculate that repeated exposures during several months may lead to the body responding to the exposure by an increase in core temperature, and that this may have a positive (i.e. inhibiting) effect on the development of features associated with Alzheimer's disease in these mice. With a whole

body SAR of 0.25 W/kg a direct heating effect of the exposure is not likely. An increase in core body temperature is not something that has been observed in other studies using long term exposures and is difficult to explain with known causes of body temperature increase. Whether this is indeed a true effect therefore needs to be confirmed in other studies, using also different levels and schedules of exposure. Follow-up studies would also have to use head-only exposures in order to better mimic the exposure in humans when using a mobile telephone. Another weakness of the study is the small group size (n=6). All in all, it is at this stage not possible to draw any conclusions with respect to any influence of using a mobile telephone on the development of Alzheimer's disease in humans.

Cancer

Cancer studies thus far have come up with variable results, but the main impression is that RF EMF does not act as tumour inducer. Some studies have found effects of RF EMF, however, on the incidence of tumours induced by other agents, i.e. a promoting effect. A recent well designed, extensive study by Tillman and co-workers investigated the effects of lifetime exposure for 20 h per day to a UMTS base station signal on the carcinogenic effects of ethylnitrosourea (ENU) (Tillmann et al., 2010). Groups of 54-60 mice were exposed to UMTS at 48 W/m^2, sham exposure, ENU alone, ENU + 4.8 W/m^2 UMTS, or served as cage controls. UMTS exposure started after conception and lasted for 24 months. No effect of 48 W/m^2 UMTS alone was observed on tumour incidences. However, exposure to the lower level of 4.8 W/m^2 UMTS enhanced the carcinogenic effect of ENU for lung tumours. The authors consider this to be a pilot study that needs to be confirmed and extended with other strains and species and exposure levels.
This is a well-designed study, using a high-quality exposure set-up and ample numbers of animals. The authors showed that the animals suffered from an infection of *Helicobacter hepaticu*s and therefore justly concluded that analysis of the liver tumour data was not warranted. It is not possible to conclude anything from this study with regards to the possible effect of UMTS exposure on humans.

Fertility

Several studies have been performed into effects of RF exposure on the reproductive system of male and female animals. (Gul et al., 2009; Kesari and Behari, 2010; Otitoloju et al., 2010; Salama et al., 2009). All these studies suffer from missing or inadequate dosimetry or otherwise inadequate experimental design. They can therefore not be used for health risk analysis.

Development

Takahashi and co-workers investigated the influence of continuous exposure of rats during pregnancy and for 120 weeks after birth on growth and development (Takahashi et al., 2010). Exposure was to 2.14 GHz W-CDMA fields for 20 h per day, as a model for exposure to base station signals. Groups of 4 dams and, after birth, 4 males and 4 females per dam, were exposed to high or low levels of EMF or sham exposed. At the high level, the whole body SAR for the fetuses and the newborn rats was 0.068-0.146 W/kg, at the low level, the SARs were about 43% of these. In the dams, growth, gestational condition and organ weights were evaluated and in the offspring survival rates, development, growth, physical and functional development, hormonal status, memory function and reproductive ability. In the second generation, embryotoxicity and teratogenicity were studied. No effect of exposure, either at high or low level, was observed on any of these parameters.

Lee et al (2009) exposed pregnant mice to a combination of two types of signals used in mobile telecommunication, a 849 MHz CDMA and a 1.95 GHz WCDMA signal (Lee et al., 2009). Two 45-min exposures separated by 15 min were given daily, from the first up to the 18th day of pregnancy. The whole-body SAR of the combined signals was 4 W/kg. After the last exposure, the animals were sacrificed and the fetuses examined for mortality, growth retardation, changes in head size and other morphological abnormalities. No effects of exposure were observed.

These studies confirm existing knowledge that even long term exposure to non-thermal levels of RF fields during pregnancy and after birth has no influence on development.

Hearing

The group of Budak in Turkey performed a series of experiments on rabbits into the effects of RF exposure on hearing (Budak et al., 2009a; Budak et al., 2009b; Budak et al., 2009c; Budak et al., 2009d). However, the results from all these studies are difficult to interpret, because of a lack of exposure data. The generator provided an output of 0.1 W, but the exposure of the animals is not provided. This is yet another example of potentially useful studies that lack proper experimental design and therefore cannot be used in health risk assessments.

Overall conclusion on animal studies

Recent studies indicate that in rodents several weeks of daily exposure of 45 min or longer to a mobile telephone signal at a SAR of 1.5 W/kg and higher may result in a response in hippocampal neurons that indicates activation in response to injury. This might have an effect on memory and cognitive functions. In previous SSM reports some behavioural effects have been reported, but a clear dose-response relationship has not been established. It is still unclear whether and to what extent rodent behaviour can be influenced by RF exposure. No inferences at all can be made from these studies with respect to any influence on human behaviour.

A study on the effect of a mobile telephone signal on the development of Alzheimer's disease indicated a possible positive effect, but it needs to be replicated with an improved design and larger groups before any conclusions can be drawn. Again, any extrapolation to humans is premature and unwarranted.

In previous SSM reports it was concluded that RF EMF does not act as tumour inducer: there is no carcinogenic effect of exposure to RF EMF alone. In some, but not all, previously described studies, RF EMF exposure was observed to enhance the incidence of tumours induced by other agents, i.e. exert a promoting effect. In a recent study this was also observed for exposure to a 3G base station signal, with a field strength higher than environmental exposures, but below the exposure limit. Without confirmation from other studies and with other species it is hard to conclude that this effect is real.

A multigeneration study on effects of a 3G base station signal on rodent development did not show any effects. This was also the case with a study employing two mobile telephone signals. These results are in accordance with previous conclusions that there doesn't seem to be an effect of non-thermal RF EMF on development.

The IEC notes that a considerable number of studies could not be evaluated because of design problems. Especially noteworthy is that often proper information on exposure is lacking. This is a waste of effort and resources. As was concluded with ELF EMF, animal studies have to use better designs in order to be useful for health risk analysis.

Human laboratory studies

The conclusions and recommendations in the previous report (IEGEMF, 2009) regarding human laboratory studies can be summarized as follows: Cognitive and EEG-based ERP (Event Related Potential) provocation studies with rather short exposures are too crude or the phenomena to be measured too small or non-existent to bring anything new to our knowledge. Therefore research should target long-term exposures and different user groups with different amounts of EMF exposure. Results from the studies on the effects of EMF on sleep are contradictory, and may be non-replicable. Thus, there is an urgent need for replications and methodologically solid studies on the effects on sleep quality and sleep (EEG) parameters. In general, EEG alpha-frequencies seem to be sensitive to modulation by some pulse-modulation frequencies of the signals (e.g., GSM mobile phones). This may be an epiphenomenon without any behavioural counterpart, and its mechanism should be studied directly in biophysics laboratories. Finally, even though there is a wide public concern, there are surprisingly few studies on EMF effects on children.

EEG

An electroencephalogram (EEG) reflects the integrated electrical activity of neurons in the outer layers of the brain. The EEG is also used to differentiate between the different sleep stages. Various descriptors of the EEG signals (frequency bands, the power of the frequency bands, (de)synchronizations, coherence between oscillations from different brain areas, etc.) have been correlated with various physiological (e.g., aging) and cognitive (e.g., alertness, attention) phenomena. EEG signals can be time-locked to behavioural events (sensory stimuli, motor responses), and via repetition of these events the signals can be averaged producing an ERP reflecting the brain events underlying the different cognition-related components.

In Australia, Croft and colleagues (2010) studied the EEG alpha band (8-12 Hz) in forty-one adolescents (13-15 year olds), forty-two young adults (19-40 years), and twenty elderly (55-70 years) with exposure to sham, GSM (maximum peak spatial SAR averaged over 10 g: 0.7 W/kg) and 3G (1.7 W/kg) exposures in a double-blind, cross-over design (Croft et al., 2010). They replicated their previous results on young adults exhibiting an increased alpha activity with exposure to GSM (Croft et al., 2008); see (IEGEMF, 2009), while in the present study no adolescents nor the elderly showed alpha changes under exposure to GSM signals, and none of the age groups to 3G. There is no clear explanation for this lack of alpha increment due to GSM exposure in adolescents and the elderly. However, the alpha increment due to GSM in young adults, reported in several studies, may be related to the pulsing in the GSM signal, as was also concluded in our previous report (IEGEMF, 2009).

In Italy, Vecchio and colleagues (2010) reported a statistically significant increment in inter-hemispheric modulation (increment of coherence) in frontal and temporal alpha rhythms (8-12 Hz) in the elderly (n=16; age range 47-84 years) but not in the young controls (n=15; age range 20-37 years) during 45 min GSM exposure (maximum SAR 0.5 W/kg) (Vecchio et al., 2010). There was a correlation between the age and the coherence in frontal alpha activity. As the authors write "A conclusive interpretation of the present results is still premature", it may be related to the changes in inter-hemispheric interactions of prefrontal cortex as a function of normal physiological aging. Unfortunately, the results by Vecchio et al. (2010) on these two age groups cannot be compared to those by Croft et al. (2010) because the authors did not report the alpha activity per se, just the changes in coherence.

De Tommaso and colleagues applied a Contingent Negative Variation (CNV) paradigm to study the effects of GSM EMF on brain electrical responses (de Tommaso et al., 2009). In

this paradigm the subject is given a warning signal, and after a short period follows a second (imperative) signal to which the subject has to respond. The CNV response is interpreted as reflecting the neuronal expectancy and the preparation to respond to the expected event. In between these two events there is a growing negativity in the scalp-recorded electric field (ERP), reflecting the expectation of the second stimulus and the preparation to respond. This negativity in the ERP can be divided into the early or initial iCNV, associated with attention and warning stimulus processing, and the late CNV, associated with preparation to respond and execution of the response. The authors evaluated the effects of GSM exposure on the iCNV response in a double-blind, crossover design in ten (20-31 years) volunteers, who were randomly subjected to three conditions (each 10 min); real GSM phone emitting electromagnetic (EM) power, sham (EM power dissipated), and sham (phone switched off). In both the real exposure and the sham (EM dissipated) conditions decrement of CNV amplitude and increasing habituation of CNV were observed, compared to sham (phone off), and the changes were distributed over the scalp. This is interpreted by the authors as reflecting the reduction of arousal and expectation of the warning stimulus. Interestingly, the effects were largest with real exposure, intermediate with sham (EM dissipated), and non-existent with sham (phone off). The authors interpret this as possibly reflecting the effect of ELF magnetic fields induced by the phones in sham (EM dissipated), and effects of ELF magnetic fields plus RF in with real exposure. The authors conclude that this is the first study dealing with the possible bio-effective role of pulsed ELF magnetic fields However, they did not report how they controlled the effect of the background noise probably present in the phones (with e.g., ear plugs, extra continuous white noise; see (Aalto et al., 2006; Haarala et al., 2003; Kwon et al., 2008).

Carrubba and colleagues (Carrubba et al., 2010) assumed that both RF and ELF magnetic pulses from the phone's battery altered the CNV triggered by acoustic stimuli. They aimed at revealing whether the 217 Hz pulses produced by the GSM mobile phones were detected by sensory transduction by "electrocells", the anatomical location (if not the existence) of which being unknown to the authors. They triggered the ERP with a 217 Hz pulse generator simulating the EMF emitted by GSM phones, using an exposure system consisting of metal plates 65 cm apart on both sides of the head. The authors showed evoked potentials in 18 of the 20 healthy (22-62 years, 13 females) volunteers, analysed by a non-linear method, whereas no evoked potentials were detected with ordinary time averaging of the EEG. The responses were slow, peaking between 250-300 ms after the trigger, depending remarkably on electrode location, being fastest at occipital sites, and 40 ms slower at adjacent parietal sites. This is a large difference for responses originating from areas right next to each other. This study should be replicated with genuine GSM mobile phones with ordinary 217 Hz pulses. Finally, the authors' claims that (i) their study might provide a possible basis for explaining how chronic phone use leads to disease, and (ii) that periodic changes in brain electrical activity causes or promotes disease, are not documented nor justified.

Since the previous report (IEGEMF, 2009) only one study on children has been published (Kwon et al., 2010a). Kwon and colleagues replicated a behaviour experiment (oddball-paradigm) previously applied to adult participants (Kwon et al., 2010b), with a group of children (17 subjects; 11-12 years) using similar exposure to GSM signals in a double-blind, crossover design. In the oddball paradigm, auditory short-term memory is studied with a flow of identical stimuli sometimes replaced by a deviant one (a change to be detected by the memory system). As with adults, no effect of GSM exposure was found. Thus, no effects on sensory memory mechanisms were observable even though the brain SAR level should have been larger in children than in adults.

Sleep

As concluded in the previous report (IEGEMF, 2009) new well-designed studies on possible sleep and sleep EEG effects with proper data analysis and statistics were very much needed especially in terms of replications of previous studies with rather vague and contradictory findings. No replications of the previous studies have appeared, but instead three new studies have been published with rather convincing results.

Danker-Hopfe et al. (2010) studied the effects of GSM-900 and UMTS on the macrostructure of sleep in a laboratory environment on 30 healthy male subjects (18-30 years) in a double-blind, randomized, sham-controlled cross-over study (Danker-Hopfe et al., 2010a). Following an adaptation night (to laboratory setting plus screening for sleep disorders), each subject was studied for 9 nights. Three exposure conditions were applied (sham, GSM-900 and UMTS). Thus, there was an 8-hour continuous RF exposure on 6 of the nights. Thirteen of 177 variables characterizing the initiation and maintenance of sleep in the GSM 900 and three in the UMTS exposure condition differed from the sham condition. To observe such a number of significant associations can be expected by chance, and thus, one can conclude that there was no negative impact of these RF signals on sleep architecture, and therefore no sleep-disturbing effect.

The same group (Danker-Hopfe et al., 2010b) also studied whether base station exposure affect sleep quality of residents in a double-blind sham-controlled randomized, balanced cross-over study. In this study, 397 residents (18-81 years, 50.9% female) from 10 sites in Germany, where mobile phone services were NOT available, were exposed to sham and GSM-900 and 1800 MHz base station signals using an experimental base station. Their sleep was monitored at their homes during 12 nights. Participants were randomly exposed to GSM or sham exposure for five nights each. Individual questionnaires on sleep disorders, sleep quality in general, attitude towards mobile phones, and morning and evening subjective sleep quality protocols were gathered. In addition, objective sleep data such as EEG recordings were collected. The real and sham exposures did not affect any of the measures of sleep quality or EEG measures although exposure difference was very small for most subjects. However, the participants with concerns about possible health risks reported sleeping worse and also the objective measurements of their sleep quality were worse during the sham-exposure nights compared to participants who were not concerned. The study does not provide any evidence for short-term physiological effects of mobile phone base stations on objective or subjective sleep quality. Furthermore, the results indicate that the mere presence of base stations (without emission of RF) can have a significant negative effect on sleep quality.

Lowden and colleagues studied effects of GSM mobile phone exposure on sleep in subjects who perceived themselves as hypersensitive to exposures from mobile phones in a double-blind experiment on self-evaluated sleepiness and objective EEG measurements during sleep (Lowden et al., 2010). 48 Subjects were exposed for 3 h under controlled conditions prior to sleep. Following exposure the duration of sleep stages 3 and 4 SWS (slow wave sleep) decreased by 9.5 min out a total of 78.6 min, and duration of stage 2 sleep increased by 8.3 min out of a total of 196.3 min compared to sham. The latencies to different sleep stages were also prolonged. The results confirmed previous findings that RF exposure increases the alpha (see EEG) range in sleep EEG, and indicated a rather weak effect on SWS in terms of increment of its onset and decrement of its length, in agreement with some earlier studies. The authors were cautious about predictions of possible health effects, but corresponding SWS

changes have been correlated with e.g. depression and burn-out. Finally, subjective rating of sleep quality was not affected and the reported differences in sensitivity to mobile phone use were not reflected in other sleep parameters.

In Austria, the Leitgeb group studied 43 individuals, who perceived themselves as hypersensitive to exposures from mobile phones (Leitgeb et al., 2008). In their own homes, the bed was shielded during the night. Three conditions were applied: true shield, sham-shield and control, during three nights each. Polysomnographic recordings were conducted and subjective sleep quality was assessed. Analyses of the EEG and subjective sleep quality data for each individual separately revealed three individuals with improvement by true shield compared to sham-shield, which would be indicative of an EMF effect. However, these results can also be expected by chance. On the other hand, six participants experienced improvement by any shield, which indicates a placebo effect. In the pooled analyses RF-EMF (true shielding) was not related to polysomnographic recordings and sleep quality.

Conclusions on EEG and sleep

Current studies confirm that the alpha frequency band in EEG is modulated by ELF and GSM EMF including low-frequency pulsing. This effect, also evident in the Croft et al. (2009) and Lowden et al. (in press) reports, seems not to be elicited by non-pulsing signals such as UMTS EMFs and has no behavioural counterparts and no effect on well-being (SSM 2009; 36). As pointed out in the previous report (SSM, 2009;36) the biophysical mechanisms of these alpha changes induced by pulsing could be well studied in animal models or in neural tissue *in-vitro* instead of such diverse and complex set-ups like human EEG measurements which themselves are sensitive to numerous other factors (i.e. attention, arousal, age etc.).
Three new reports on sleep and sleep EEG have been published with rather convincing results based on large numbers of participants and well controlled designs. Based on these studies it appears that EMF exposure does not affect the subjective well-being, whereas signs of slight changes in some sleep parameters were found. The sleep EEG study again confirmed the effect of GSM EMF on the EEG alpha band.

Cognition

In a recent review, Van Rongen and colleagues covered a considerable amount of laboratory studies on the effects of RF EMF on cognitive functions (van Rongen et al., 2009). The conclusion was that no consistent significant effects on cognitive performance in adults have been observed. Furthermore, they conclude that effects in children did not differ from those in healthy adults. The previous SSM report (IEGEMF, 2009) also concludes that as earlier studies have been replicated with more conservative statistical criteria in order to avoid false positive findings, earlier findings have not been replicable, and there are no measurable cognitive effects based on behavioural measures available today.

In a systematic review and meta-analysis, Valentini and colleagues concluded that mobile phone EMF does not seem to induce cognitive and psychomotor effects (Valentini et al., 2010). They also report a sharp increase in null results in publications between 2005 and 2008, which they propose "may be accounted for by greater attention given to methodology, such as self- and hetero-replication of positive results and the application of stricter statistical methods (e.g., Bonferroni correction for post hoc multiple comparisons)" and they also found indications of sponsorship bias. They recommend that more studies be done, but with a proper design, i.e. fully blinded and with adequate number of subjects.

Since the previous SSM report (IEGEMF, 2009), only one new report on cognition has appeared. Riddervold and colleagues studied the effects of TETRA handsets on human cognitive functions and symptoms with a randomized, double-blind, cross-over paradigm (Riddervold et al., 2010). The participants were 53 male volunteers composed of employees from the emergency services (25-53 years). The computerized cognitive tests were Reaction time (simple and 5-choice reaction time) and spatial span (visual-spatial working memory) from the CANTAB test battery, digit span (verbal working memory) from WAIS, and Trail Making B (psycho-motor speed, attention). A computerized Visual Analog Scale (VAS) was used to assess self-reported subjective symptoms. Compared with sham conditions, a 45 min continuous exposure to TETRA had no statistically significant effects on cognitive performance or on self-reported perception of symptoms in normal healthy males. The participants were also not able to tell whether they were exposed or not.

To summarize, effects during short exposures are not demonstrable with present cognitive measures either in adults or children. There is a need for studies involving longer exposures, especially in children.

Symptoms

In addition to the studies on self-reported symptoms and well-being discussed above (Leitgeb et al., 2008; Lowden et al., 2010; Riddervold et al., 2010) the following papers on this topic have been published.

Nieto-Hernandez et al (2010) investigated the effect of TETRA handsets on symptoms in 60 TETRA users with and 60 without symptoms in a randomized single-blind crossover study (Nieto-Hernandez et al., 2010). They applied three exposure conditions at a SAR_{10g} of 1.3 W/kg (385 MHz continuous wave, TETRA and sham). None of the symptoms (headache, fatigue, dizziness, nausea, sensations of warmth or burning on skin, skin itching, tingling, stinging or numbness, feeling irritable or anxious or depressed, difficulty concentrating or thinking) was related to exposure except skin itching which was decreased during continuous wave exposure.

Wallace et al. (2010) studied the ability to detect TETRA base station signals in a group of fifty-one self-reported electrically hypersensitive individuals and 132 age- and sex-matched controls in a randomized double-blind provocation study (Wallace et al., 2010). VAS scales and symptom scales were used to measure subjective well-being. Physiological measures were blood volume pulse, heart rate and skin conductance. There were six double-blind on-off judgments following an open provocation trial (TETRA and sham), where both the experimenter and the subject knew whether the device was on or off. There was no difference in any measures between TETRA and sham (no signal) for either controls or electrically hypersensitive participants, and neither group could detect the presence of the TETRA signal at rates greater than chance. However, in the non-blind condition, the self-reported electrically hypersensitive individuals reported feeling worse and experienced more severe symptoms during TETRA compared with sham. Significant worsening of symptoms in the open provocation tests was also observed in the non-EHS collective, however, to a lower extent. This result suggests that the adverse symptoms experienced by the electrosensitive individuals are due to the belief of harm (nocebo-effect) from TETRA-base-stations rather than to the low-level RF exposure itself.

Nam and colleagues studied the ability of 18 self-reported electrically hypersensitive and 19 control subjects to perceive the existence of the EMF (CDMA), as well as subjective symptoms (Nam et al., 2009). Also several physiological reactions (heart rate, respiration, heart rate variability) were measured. No effects were found in either of the groups.

Landgrebe and co-workers studied the prevalence of tinnitus, the "ringing ears" with no known mechanism, in 69 self-reported electrically hypersensitive subjects and 80 controls. 50.7% of the hypersensitive subjects in contrast to only 17.5% of the controls reported to experience tinnitus (Landgrebe et al., 2009). There was no difference between the groups with regard to the severity or duration of tinnitus. The amount of cell phone use did not have any association with the tinnitus. The authors discuss the possibility for an individual vulnerability to both self-reported electrical hypersensitivity and tinnitus.

Others

Eye-movements (e.g., saccades) are objective measures for involuntary and voluntary attention, and they are controlled largely by the same brain areas as are involved in visuospatial attention. It has been previously reported that 30 min mobile phone use does not affect performance in simple visually guided and memory-guided saccades (Terao et al., 2007), suggesting that cortical mechanisms for saccades and attention are not affected by MP EMF. Okano et al. (2010) further investigated whether such effects could be seen in more demanding eye-movement paradigms, requiring both initiation and inhibition (both important components of executive functions and working memory) of saccades depending on the behavioural context (Okano et al., 2010). This double-blind counterbalanced cross-over study (10 subjects; age 35.2 +/- 7.5 years) showed that the pulsed EMF delivered through a handset, mimicking the maximum EMF output by ordinary Japanese mobile phones, did not induce any statistically significant differences in inhibitory control of saccades compared to the sham, whereas in two of the tasks faster reactions were measured during both 30 min exposure and 30 min sham exposure. Thus, there was no effect of pulsed EMF on the more complex saccade tasks.

The Mizuno group used positron emission tomography (PET) to study regional Cerebral Blood Flow (rCBF) in 9 subjects before, during and after a 30 min exposure to 3G EMF (2 W/kg) in a single-blind, randomized cross-over design (Mizuno et al., 2009). Contrary to previous PET-studies, e.g., (Aalto et al., 2006; Haarala et al., 2003), the subjects did not perform any cognitive task during the scanning. No effects of the 3G exposure were found. Thus, there is an interesting difference between the Mizuno et al. (2009) study and previous PET studies on EMF effects on blood circulation in the human brain, which parallels the difference observed in EEG studies in the alpha-band changes due to 2G but not due to 3G signals (see above). More studies are needed to elucidate this difference.

Overall conclusions and recommendations

Several high-quality papers have been published on the effects of mobile phone EMF on sleep quality, parameters, and sleep EEG, helping to solve some of the questions produced by the previous, contradictory data. EEG studies again show effects of GSM mobile phone EMF (i.e. a pulsed signal) on the alpha-band. This phenomenon should be further studied in well controlled experimental set-ups (in terms of dosimetry and EEG recording) with animal models and neural tissue cultures, in order to see how the electrical activity of neuronal networks is affected by the GSM and 3G signals (pulsed or non-pulsed). Imaging (e.g. PET) studies have shown promising, although variable, results possibly due to the difference between GSM and 3G signals. Further studies will need to be well-designed and have an

adequate number of participants to obtain good statistical power. There are some modern neuroscientific methods (e.g. brain imaging and brain stimulation; see the previous report (IEGEMF, 2009) that should be used to address the issue of perceived electrical hypersensitivity. Finally, comprehensive studies on long-term exposures, and especially studies on children are still lacking.

Recent epidemiological studies

Mobile phone studies

Interphone

Since the publication of our previous report, the pooled analysis of the INTERPHONE study about the glioma and the meningioma risk in relation to use of mobile phone has been published (INTERPHONE). In this analysis, 2409 meningioma, 2708 glioma cases and matched controls from 13 countries have been included. Eligible cases were between 30 and 59 years and diagnosed during study periods of 2-4 years between 2000 and 2004. Use of mobile phone was assessed retrospectively by means of face-to-face interviews with the study participants or with a proxy if participants had died or were too ill to be interviewed. The same core protocol was used in all countries. Participation rates were 78% among meningioma cases, 64% among glioma cases and 53% among controls.

All study participants who had an average of at least one call per week for a period of at least 6 months were considered regular mobile phone users. For regular users a reduced odds ratio (OR) was seen for glioma (OR 0.81; 95% confidence interval (CI) 0.70–0.94) and meningioma (OR 0.79; 95% CI 0.68–0.91). Study participants whose first mobile phone use was at least 10 years ago did not show an increased glioma or meningioma risk. In terms of cumulative call time, all ORs were <1.0 for all deciles of exposure except the highest (10^{th}) decile of recalled cumulative call time (≥1640 h). For this exposure group the OR was 1.40 (95% CI 1.03–1.89) for glioma, and 1.15 (95% CI 0.81–1.62) for meningioma. Regarding cumulative number of calls, the highest exposure group did not show an increased glioma or meningioma risk.

Overall the results were not conclusive and various methodological limitations are discussed in the paper and by others (Peres, 2010; Saracci and Samet, 2010). The main concerns are participation and recall bias.
Participation bias: As study participation was not complete, participation bias would occur if the likelihood of participation is related to both, disease and exposure status. For instances, if among controls mobile phone users were more likely to participate than non-users and if this is not the case among patients, this would create spurious protective effect estimates. In order to evaluate participation bias, non-responder interviews were conducted in 9 out of 11 centres. These interviews indicated that indeed among both cases and controls, mobile phone users were more likely to participate in the study than nonusers (Vrijheid et al., 2009b). As refusal was more common among controls than cases, it was estimated that non-participation bias may have led to a reduction in the ORs for regular use of 5–15%, which is less than actually observed. In appendix 2 of the main paper (INTERPHONE, 2010), an attempt was undertaken to crudely correct the risk estimates for participation bias by omitting the non-users from the dataset and by using the lowest exposure category as the reference. As a result, most of the OR's for meningioma stayed below unity whereas for glioma most OR's increased above unity. Statistically significant increased glioma risks were found for persons who started to use their phone 2-4 years prior to diagnosis (OR=1.7; 95% CI 1.2-2.4), 5-9 year prior to

diagnosis (OR=1.5; 95% CI 1.1-2.2) as well as persons who started to use their mobile phone more than 10 years prior to diagnosis (OR=2.2; 95% CI 1.4-3.3). In terms of cumulative call time, the OR for glioma did not show an increase with exposure, but the OR for the highest category (>1640 hours) was statistically significantly increased (OR=1.8; 95% CI 1.2-2.9). The results of these analyses would indicate a truly increased risk, if participation bias is the only explanation of the decreased risks of the main analyses and if participation depends only on the user status (user vs. non-users) but does not vary between various levels of exposure. This has not to be necessarily correct and there is actually some indication that participation bias may affect the distribution of time since first use (Table 4 in (Vrijheid et al., 2009b)). Furthermore, there was no trend evident that centers with low participation rates had lower OR's than centers with higher participation rate, where participation bias cannot be large. This indicates that participation rate may not be the sole reason for reduced OR of the main analyses and it undermines the assumption on which the analyses of appendix 2 are based. In appendix 2 various additional arguments are presented that speak against the validity of the results. Most importantly, the considerably increased glioma risk after 2-4 years of mobile phone use contradicts recent studies on time trends of brain tumour incidence (Deltour et al., 2009; Inskip et al., 2010) (see below).

Recall bias: The second main limitation is possible recall bias. If cases tended to overestimate their exposure more often than controls, this could create a spurious association. The most extreme exposure category could also be affected, if cases show a higher variance in their estimated exposure (even without overestimation of exposure on average). According to a comparison of self-reported mobile phone use with operator-recorded data in a sample of INTERPHONE participants from Australia, Canada and Italy, little differential exposure misclassification between cases and controls were found on average. However, in the highest category of cumulative number of calls exposure overestimation was more pronounced in cases than in controls (Vrijheid et al., 2009a). Furthermore, the ratio of self-reported phone use divided by recorded phone use increased with increasing time before the interview in cases but not in controls. Cases also had a higher variance of these ratios than controls. Such a pattern could explain an increased risk in the most extreme exposure categories. However, the validation study is only based on a subset of the INTERPHONE study participants. The number of subjects with long-term data was relatively small and recall could only be assessed for a period of up to 4-6 years at the most.

In the view of the inherent methodological limitations of case-control studies based on self-reported exposure data, exhaustive sensitivity analyses were conducted by the INTERPHONE study team, in order to evaluate consistency of the findings. For meningioma, little evidence was obtained for a relation with mobile phone use and these results are not further discussed. For glioma, however, the results of the sensitivity analyses were somewhat contrary, some of the analyses pointing to an increased risk whereas other results did not. Most remarkable findings that may support an association between mobile phone use and glioma were:

- OR in the highest exposure decile of cumulative use was larger for tumours in the highly exposed temporal lobe (OR 1.87; 95% CI 1.09–3.22) than in the lower exposed parietal or frontal lobes (OR 1.25; 95% CI 0.81–1.91) or tumours in other locations (OR 0.91; 95% CI 0.33–2.51).
- The ratio between ipsi- and contralateral used increased steadily with increasing cumulative number of calls. This is in line with a reasonable exposure-response association. However, for time since start of use and for cumulative call time the highest ratios were observed in the category with the lowest exposure. This does not

support a causal association and indicates the presence of recall bias when reporting side of phone use.

- ORs in the highest decile of cumulative call time were larger for analogue phones (OR 1.95, 95% CI 1.08–3.54) than for digital phones (OR 1.46, 95% CI 0.98–2.17). This is in line with an exposure-response association as the output power of analogue phones is larger than for digital phones. However, the difference between the two OR's is small and not statistically significant. There might also be a difference in recall bias as analogue phones were usually used during more distant time periods than GSM phones.

On the other hand, several results do not support an exposure-response association:

- There was no upward trend in the ORs for the first nine deciles of cumulative call time. This is an unexpected exposure-response pattern. Moreover, no increased risk was observed in the highest exposure category of time since start of use and of cumulative number of calls.
- Increased risk in the highest exposure decile of cumulative call time was more pronounced in short term users, who started to use phones 1-4 years before reference date than in long-term users (≥ 10 year) (OR of 3.77 vs. 1.34). This is not in line with a priori expectation about latency and induction time. Such a rapid and sharp risk increase should have been observed in incidence time trends data (see below).
- The OR for the highest exposure decile of cumulative call time dropped from 1.40 to 1.27 when subjects who reported >5 h/day were excluded. This indicates that implausible amount of use was more often reported by cases than controls. Actually glioma cases had a higher proportion of proxy respondents, a higher number of imputations for missing values, and a higher proportion of subjects judged by their interviewer to be non-responsive or having poor memory.

In conclusion, the INTERPHONE study could not finally resolve whether use of mobile phone causes brain tumours. At least, a short term risk can be excluded with a high degree of certainty, but uncertainty still remains regarding very intensive and long-term use.

Other brain tumour studies

Since the publication of the previous report, Hardell et al. published two additional papers from their case-control study that included cases diagnosed between 1997 and 2003 (Hardell and Carlberg, 2009; Hardell et al., 2010a). One of these analyses is a mere re-analysis of previously published data with a focus on the age-dependent brain tumour risk (Hardell and Carlberg, 2009). Results stratified on age at first use have been presented previously (Hardell et al., 2006a, b), but the new paper includes some more detailed analyses. The study consists of 905 (participation rate: 90%) cases with malignant brain tumours, 1,254 (88%) cases with benign tumours and 2,162 (89%) population-based controls. In the re-analysis highest risk was observed for participants who started to use mobile phones at <20 years. For astrocytoma the OR was 5.2 (95% CI 2.2-12) for mobile phone use and 4.4 (95% CI 1.9-10) for use of cordless phone. For acoustic neuroma the OR was 5.0 (95% CI 1.5-16) for participants who started to use the phone below 20 years of age. In addition, the incidence rate of brain tumours in Sweden was analysed for the period of 1970-2007. During this period, the annual age adjusted brain tumour incidence increased by 0.28% (95% CI 0.04-0.52). For men, the increased incidence occurred during the early periods before the time when mobile phone use had become widespread. For women, the increase started already in the period 1970-1979, and was seen in all studied time periods. For astrocytoma in the ages >19 years, there was no change in the incidence looking over the entire time period 1970-2007. During the four

decades, the astrocytoma incidence fluctuated up and down; it was reduced in the 1970s, increased in the 1980s, reduced during the 1990s, and increased during 2000-2007. For acoustic neuroma in the same age group the incidence increased by 2.12% (95% CI 1.22-3.02) for the period of 1970-2007. Most of the increase was seen during the 1980s; during the period 2000-2007 there was a decrease in the incidence (-7.10%; 95% CI -12.4 to -1.42). An analysis by region suggests that recent temporal incidence increase is restricted to the Gothenburg region. In the Gothenburg region, age adjusted incidence was roughly twice as high as in the Stockholm county. Sweden is a small country and there is a large random variation of the incidence from year to year for rare diseases. Such random variation is even more pronounced when restricting the analyses to single regions and short time periods. Thus, the recent increase in the Gothenburg region does not allow firm conclusions. Indeed, looking at the yearly incidence data provided online by the Swedish Cancer registry (http://www.socialstyrelsen.se/statistik/statistikdatabas) does not give the impression that the brain tumour incidence is increasing since the introduction of mobile phones, which is in line with more comprehensive analyses (Deltour et al., 2009; Inskip et al., 2010).

In the other report by the Hardell group (Hardell et al., 2010a), a new analysis was conducted which was restricted to malignant brain tumours of deceased cases and controls that had not been included in the previous analyses. Two different control groups were recruited: one with controls that had died from another type of cancer than brain tumour and one control group that had died from other diseases. Exposure was assessed by a written questionnaire that was sent to the next-of-kin for both cases and controls between November 2006 and August 2008. Response was obtained from 346 (participation rate: 75%) cases, 343 (74%) cancer controls and 276 (60%) other controls. About one third of the cases and one quarter of the controls were mobile phone users. Assuming a latency of 10 years yielded an OR of 2.4 (95% CI 1.4–4.1) for mobile phone users compared to non-users. In the highest exposure group (>2000 h) OR for analogue phone user was 5.1 (95% CI 1.8–14.0) and for digital phone user 3.4 (95% CI 1.5–8.1). No increased risk was seen in cordless phone users. The results of this study are in line with previous results from the same study group about non-deceased cases. A serious limitation in this study is the large time gap between diagnosis and time of the interview with the relatives. Exposure misclassification is likely to be substantial, and the possibility of recall bias cannot be excluded.

A few ecological studies have analyzed temporal and spatial trends of the brain tumour incidence pattern as suggested in the new research agenda for radiofrequency fields published by the World Health Organization (WHO, 2010).
A pooled analysis of the national cancer registry data from Denmark, Finland, Norway and Sweden covered the period from 1974 to 2003 (Deltour et al., 2009). In this period, brain tumour incidences increased significantly, most pronounced for meningioma in women after the early 1990s (3.8% per year; 95% CI 3.2% to 4.4%). As time trends in more recent period would be indicative for an increased risk of mobile phone use, joinpoint analysis with not constraints on the positions of the joinpoints were conducted. This analysis did not yield changes in incidence rate trends from 1998 to 2003. Whereas the overall incidence increase between 1974 and 2003 is believed to be mainly attributable to improved diagnosis, the lack of a detectable trend change in the more recent period, and in the age-groups with the highest prevalence of mobile phone use, suggesting that the brain tumour risk of mobile phones after an induction period of 5–10 years is absent or too small to be detected in this study population.

A similar analysis was conducted by Inskip et al. (2010) for the United States by using data collected by the Surveillance, Epidemiology and End Results (SEER) Program (Inskip et al., 2010). They estimated time trends separately for 1977–1991 (introduction of computerized tomography, CT, and magnetic resonance imaging, MRI) and for 1992-2006, when mobile phones became more prevalent. In total, 38,788 brain cancers were diagnosed during the 30 year period, of which more than 95% were gliomas. In the more recent period gender specific time trends for all age groups were downward or flat, except among women aged 20–29 years, where a statistically significant increasing trend was observed (4.3% per year, 95% CI 1.9–6.7). Further analyses showed that this increase was due to rising incidence of frontal lobe tumours but no trend was observed for temporal or parietal lobes. The frontal lobe is less exposed by mobile phones than the temporal lobe. Thus, the observed increase for women is unlikely to be caused by mobile phones.

Overall conclusions on brain tumour studies

Based on the results from the pooled analyses of the INTERPHONE study (INTERPHONE, 2010) and two studies evaluating data from high-quality cancer registries (Deltour et al., 2009; Inskip et al., 2010) a short term risk of mobile phone use can be excluded with a high degree of certainty. If mobile phone use increased the brain tumour risk by 50% or more, one would roughly expect to observe an increase in the brain tumour incidence of 30% or more since the introduction of mobile phones assuming a prevalence of mobile phone use of 60%. Such an increase would be clearly detectable unless compensated by a very strong preventive factor that was introduced at the same time as mobile phones. So far, nobody has suggested such a preventive factor. It is particularly hard to imagine that risk increases of 100% or more that have been reported in some studies for specific age groups would not be detectable in brain cancer incidence data.

A potential risk for a specific histological tumour entity would be harder to detect in time trends data as the number of cases is small and thus time trends are more fluctuating. Similarly, identification of a potential long-term effect is more challenging since the prevalence of long-term users is smaller. In particular, no data are available for very long exposure periods of more than 20 years. However, even if induction time is long on average, incident cases with shorter than average induction periods have to be expected as the latency distribution will scatter around the mean induction time. Thus, if use of mobile phones was a substantial long-term risk, incidence data should indicate increasing rates by now. Though, a small risk increase may be still undetectable.

Reproductive studies

Data from a Spanish birth cohort that was established between 2004 and 2006 were used to investigate the association between prenatal exposure to mobile phones and neurodevelopment at 14 months (Vrijheid et al., 2010). A questionnaire about mobile phone use was completed by mothers in week 32 of the pregnancy. The Bayley Scales of Infant Development was used to test neurodevelopment of their children at age 14 months. Data from 530 children were analyzed. The study provided little evidence that mental or psychomotor development is affected by the mobile phone use of the mother during pregnancy. The advantage of this study is its prospective design, i.e. exposure information was collected prior to the outcome measurement. Thus, the results cannot be affected by recall bias. Recall bias may explain the result of the Danish National Birth Cohort Study that reported an association between prenatal and postnatal mobile phone exposure and behavioural problems in children since exposure and outcome was assessed at the same time when children reached the age of seven (Divan et al., 2008). On the other hand, the Spanish

study was considerably smaller than the Danish study and subtle effects of prenatal mobile phone exposure might have been missed.

Other mobile phone studies

The association between tinnitus and mobile phone use has been investigated in an Austrian hospital-based case-control study (Hutter et al., 2010). 100 consecutive patients aged between 16 and 80 years have been enrolled between November 2003 and November 2004. For each case, an age and sex matched control patient without any concomitant condition related to tinnitus was randomly selected from the daily lists of outpatients of the same hospital. Use of mobile phone was assessed using a written adaption of the INTERPHONE questionnaire. Only exposure prior to the date of first occurrence of tinnitus was considered in cases and the corresponding controls. The OR for mobile phone use at the same side as the tinnitus was 1.37 (95% CI 0.73–2.57). A significantly increased OR was observed if duration of use was four or more years (OR 1.95; 95% CI 1.00–3.80). Separate analyses for contralateral use of mobile phones yielded similar results as the ipsilateral analyses except the increased risk of long-term users, which was not observed for contralateral use. Participation rate was high (96% for cases, 93% for controls). Self-reported exposure assessment is a drawback of this study. Some confounding factors were included in the study and did not affect the risk estimates much. However, the authors discuss the possibility of residual confounding from hearing impairment induced by hearing loud music with portable players. Use of portable players may be related to mobile phone use. Apart from radiation effects, alternative non-radiation pathways are discussed for the observed effect such as modulated blood flow when pressing the mobile phone to the ear, cranio-cervical manipulations of the head when using a mobile phone or increased noise exposure from the mobile phones.

The association between cognitive functions in adolescents and mobile phone use was assessed in a prospective cohort study which comprised a baseline examination of year 7 students and a 1-year follow-up (Thomas et al., 2010a). 236 students participated in both examinations consisting of a computerized test battery and the Stroop Color Word test. Use of mobile phone was assessed by a modified version of the INTERPHONE questionnaire. Stroop test and accuracy of the tests from the battery were not related to mobile phone exposure. Participants with a high baseline mobile phone exposure showed less reduction in response time over the 1-year period in various computerized tasks. However, results were comparable for number of SMS and number of voice calls. In addition, increase in the number of voice calls between baseline and follow-up was related to changes in the response time in two out of nine tasks. Further analyses indicated that observed changes occurred mainly in those who had fewer voice calls and SMS at baseline. Thus, according to the authors, the observed changes over time may relate to statistical regression to the mean and not represent the effect of mobile phone exposure. Self-reported exposure data is a limitation in this study. As RF-EMF exposure to the head is negligible when sending SMS, one would not expect an effect of SMS on cognitive function unless number of SMS is well correlated with the number of calls (correlation coefficient not reported in the paper).

In a Swiss cross-sectional study, self-reported sleep disturbances and excess daytime sleepiness was not related to self-reported and operator-recorded mobile phone use (Mohler et al., 2010). 1212 participants were included in the analysis of self-reported mobile phone use (participation rate: 37%). Thereof, 453 participants gave consent that their mobile phone connection data of the previous six months could be obtained from their operator. After controlling for various potential confounders, neither excess daytime sleepiness (OR=1.03; 95% CI 0.62–1.69) nor sleep disturbances (OR=0.64; 95% CI 0.31–1.28) occurred more often

in the highest exposure decile of self-reported mobile phone use compared to the low exposure group (<median). These results were confirmed with the operator data: OR for excess daytime sleepiness was 0.91 (95% CI 0.39–2.11) and OR for sleep disturbances was 1.03 (95% CI 0.32–3.30). This is the first study addressing non-specific symptoms by using objective operator-recorded mobile phone use data. The low participation rate is a limitation although phone interviews with 634 non-responders do not indicate substantial selection bias in this study.

A Swedish cross-sectional study aimed to investigate effects of mobile and cordless phone use on the blood-brain (Söderqvist et al., 2009b) and the blood-cerebrospinal fluid barrier (Söderqvist et al., 2009a). From 1000 randomly selected individuals aged between 18 and 65 years and living in Örebro, 31% participated in the study. Blood samples were taken at the hospital. As a putative marker of blood-brain barrier dysfunction serum S100B was determined and as a potential marker of the blood-cerebrospinal fluid barrier dysfunction transthyretin in the blood was measured. Exposure to mobile and cordless phones was obtained by a written questionnaire. Serum S100B levels were not found to be related to mobile or cordless phone use except in one small subgroup analysis where latency of UMTS use was positively correlated with S100B levels in men (p=0.01, n=31) but not in women (Söderqvist et al., 2009b). Transthyretin levels were not related to most of the analyzed exposure proxies such as mobile phone use (yes/no, considering 0, 5, or 10 years of latency) or cumulative hours of cordless or mobile phone use (Söderqvist et al., 2009a). Time since first use of mobile phones was positively correlated to transthyretin levels in men but not in women. In women, a short term effect was reported: the shorter the time period between blood withdrawal and the most recent phone call, the higher were the transthyretin levels. However, minutes of mobile phone use on the day of giving blood was not related to transthyretin.
The low participation rate and self-reported exposure data are a limitation of this study. Furthermore, the absence of a consistent exposure-response pattern for both markers, and effects confined to subgroup analyses, does not provide strong support for a causal association.

In a collective of 62 persons aged 18–30 years who were enrolled for an experimental study, questionnaire data about their past mobile and cordless phone use were compared with the serum β-trace protein in their blood levels (Hardell et al., 2010b). β-trace protein is the key enzyme in the synthesis of prostaglandin D_2, an endogenous sleep-promoting neurohormone in the brain. Linear regression models adjusted for age revealed a non-significant negative correlation with cumulative hours of mobile and cordless phone use (p=0.16) and a significant negative correlation with years since first use of mobile or cordless phones (p=0.03). The study is small, potential confounding factors such as circadian variation were not considered in the analysis, and the exposure data are self-reported, thus, the results have to be interpreted with caution.

Transmitter studies

The IEG has looked at studies on transmitters and cancer risk previously in 2003, 2006, and 2009. Almost all transmitters in those studies were radio and TV stations. Only in 2009 had studies with reasonably good exposure assessments and other validity aspects been presented, one in Korea and one in Germany. None of these indicated any association between RF exposure and cancer risk. While the risk of cancer from such exposure cannot be excluded based on these results, the IEG noted that at present there were no data neither from

epidemiologic research, nor from experimental research to indicate the existence of such a risk.
Since then the first full scale epidemiologic study on mobile phone base stations and cancer risk has been published (Elliott et al., 2010). The study investigated cancer risk in children and exposure to mothers during pregnancy. This is a nationwide study in the UK that took advantage of the cancer registration system and of a digitized geographical information system including data on base station sites. The critical part in such a study is the exposure assessment. The authors used three approaches to exposure assessment, namely distance between nearest base station and birth address, the total power output from all base stations within 700 meters of the birth address, and an estimated power density based on distance, characteristics of the base station, and some geographical characteristics. The study found no indications for an association between childhood cancer risk and RF exposure from the base stations with any of the proxies for exposure used in the study. The study is big and, because of the design, selection bias or confounding seems unlikely to impact the results. However, as the authors note in their discussion of the findings, the validity of the exposure proxies need further exploration and so does the potential impact of the fact that sources of RF other than macro cell base stations could not be accounted for.

In the Swiss cross-sectional study on self-reported sleep quality discussed above (Mohler et al., 2010), neither self-reported sleep disturbances nor excess daytime sleepiness was related to modelled RF-EMF exposure from fixed site transmitters in the bedroom of 1212 participants. Furthermore, estimated exposure at night considering also indoor sources such as DECT phone base stations, was not related to sleep quality.

In a German study of 3022 children (8-12 years) and adolescents (13-17 years) (participation rate 52%), RF exposure measured with a dosimeter was not correlated with reported symptoms (Heinrich et al., 2011). Exposure assessment was based on a 24-hour measurement of field strength using the portable Maschek ESM-140 device recording readings every second. The frequency range covered GSM 900, GSM 1800, UMTS 2100, DECT and WLAN signals. Acute symptoms (headache, irritation, nervousness, dizziness, fear, sleeping problems and fatigue) were quantified on a four-point Likert scale. No consistent relation between exposure (divided into quartiles) and any of the symptoms was found. Limitations of the study include the incapability of the measurement device to record while inert (i.e. during night). The exposure levels were low (below 1% of the ICNIRP guideline).
In the same data (Thomas et al., 2010b) an association between behavioral problems and daytime personal RF-EMF exposure was observed in adolescents (4th vs. 1st quartile of exposure: OR=2.2; 95% CI: 1.1-4.5) but not in children (OR=1.3; 95% CI: 0.7–2.6). This was mainly due to the subscales conduct problems (OR=3.7; 95% CI: 1.6–8.4) and hyperactivity (OR=2.1; 95% CI: 0.9–4.8).

In conclusion, based on this and on the previous studies on transmitters and cancer one cannot exclude the existence of cancer risks with any certainty, but so far no scientific data indicate the existence of such a risk.

WHO Research Agenda for Radiofrequency fields

A new Research Agenda for radiofrequency (RF) fields has been published in August 2010 by the World Health Organization (http://www.who.int/peh-emf/research/agenda/en/index.html). This document represents an update to previous WHO research agendas on RF fields developed in 1997, 2003 and 2006. These documents have served as blueprint for a number of

national research programmes, as shown by the uptake of the research priorities among funding agencies and researchers alike.

With new scientific developments undertaken over the past 3 years and the completion and renewal of several national research programs, an update of the RF Research Agenda was deemed necessary. The document was undertaken with the input of an ad hoc committee of invited scientific experts. A technical consultation was held in February 2010 to develop a list of research recommendations based on the results of an international survey of over 400 experts with diverse backgrounds and viewpoints.

Other relevant actions to focus research priorities on RF and health have been made by the International Commission on Non-Ionizing Radiation Protection in its recent review of RF research (ICNIRP, 2009) as well as by several national agencies (AFSSET, 2009; NRC, 2008) and international organizations (EMF-NET, 2009; SCENHIR, 2009).

The new WHO Research Agenda documents gaps in knowledge needing further targeted research and identifies specific research needs in basic science relevant to health risk assessment, as well as public concern and risk communication in meeting public health needs. The document is organized by two main themes: (i) needs for health effects research; and (ii) needs for social science research. A brief summary of ongoing research is provided for each type of health effect research study, along with overarching issues relevant to the design and analysis of future studies. The research priorities for the different areas of work are provided below along with their level of priority (high or other) research needs:

Epidemiology

- Prospective cohort studies of children and adolescents with outcomes including behavioural and neurological disorders and cancer (birth cohorts have been established in several countries and could be used for this purpose) - **High**
- Monitoring of brain tumour incidence trends through well-established population-based cancer registries, if possible combined with population exposure data - **High**
- Case-control studies of neurological diseases provided that objective exposure data and confounder data are available and reasonable participation is achieved - **Other**

Human studies

- Further RF EMF provocation studies on children of different ages - **High**
- Provocation studies to identify neurobiological mechanisms underlying possible effects of RF on brain function, including sleep and resting EEG - **High**

Animal studies

- Effects of early-life and prenatal RF exposure on development and behaviour - **High**
- Effects of RF exposure on ageing and neurodegenerative diseases - **High**
- Effects of RF exposure on reproductive organs- **Other**

Cellular studies

- Identify optimal sets of experimental tests to detect cellular response after exposure to new RF technologies and co-exposures of RF EMF with environmental agents- **Other**
- Further studies on the influence of genetic background and cell type: possible effects of mobile phone type RF exposure on a variety of cell types using newer, more sensitive methods less susceptible to artefact and/or bias- **Other**

Mechanisms
- None

Dosimetry
- Assess characteristic RF EMF emissions, exposure scenarios and corresponding exposure levels for new and emerging RF technologies; also for changes in the use of established technologies - **High**
- Quantify personal exposures from a range of RF sources and identify the determinants of exposure in the general population - **High**
- Monitoring of personal exposure of RF workers- **Other**

Social science research (no priorities given)
- Investigate the determinants and dynamics of RF EMF-related health concern and perceived health risks
- Investigate the effectiveness of different formats for communicating scientific evidence regarding health effects of RF EMF exposure and risk information to the public
- Investigate whether and how people's perception of RF EMF health risks can affect their well-being
- Investigate how RF EMF technologies have been handled in a larger social context

WHO Environmental Health Criteria Monograph on radiofrequency fields

Health risk assessments related to chemical, biological and physical agents have been published by WHO in the Environmental Health Criteria (EHC) series (http://www.who.int/ipcs/publications/ehc/en/). For over 25 years, WHO has addressed possible health effects from exposure to electromagnetic fields through monographs on extremely low frequency (ELF) fields (1984), static and ELF magnetic fields (1987), and radiofrequency (RF) fields (1993).

In the last few years, three monographs spanning the 0-300 GHz EMF frequency range have been planned: static fields (0Hz), ELF fields (up to 100 kHz) and RF fields (100 kHz – 300 GHz). So far, the EMF Project has developed the first two volumes on Static Fields (2006, http://www.who.int/peh-emf/publications/reports/ehcstatic/en/index.html) and ELF fields (2007, http://www.who.int/peh-emf/publications/elf_ehc/en/index.html). These documents were developed following the publication of the IARC monograph on Non-Ionizing Radiation, Part 1: Static and ELF fields (2002). While the IARC monographs provide a hazard identification regarding cancer, the EHCs represent a health risk assessment of all published health endpoints, using the four classical steps of (i) hazard identification, (ii) exposure assessment, (iii) dose-response assessment and (iv) risk characterization.

The next major task in this evaluation process is the health risk assessment of radiofrequency fields. The document will update the review of scientific literature on the health effects of RF fields commissioned to ICNIRP in 2005 and published in 2009. The timing of the EHC development is contingent on the release of the expected IARC monograph on *Non-Ionizing Radiation, Part 2: Radiofrequency (RF) electromagnetic fields and radar (including mobile telephones)*. Following the release of the INTERPHONE study earlier this year, the IARC monograph meeting for vol. 102 on RF will be held at the end of May 2011.

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2010:44

The Swedish Radiation Safety Authority has a comprehensive responsibility to ensure that society is safe from the effects of radiation. The Authority works to achieve radiation safety in a number of areas: nuclear power, medical care as well as commercial products and services. The Authority also works to achieve protection from natural radiation and to increase the level of radiation safety internationally.

The Swedish Radiation Safety Authority works proactively and preventively to protect people and the environment from the harmful effects of radiation, now and in the future. The Authority issues regulations and supervises compliance, while also supporting research, providing training and information, and issuing advice. Often, activities involving radiation require licences issued by the Authority. The Swedish Radiation Safety Authority maintains emergency preparedness around the clock with the aim of limiting the aftermath of radiation accidents and the unintentional spreading of radioactive substances. The Authority participates in international co-operation in order to promote radiation safety and finances projects aiming to raise the level of radiation safety in certain Eastern European countries.

The Authority reports to the Ministry of the Environment and has around 270 employees with competencies in the fields of engineering, natural and behavioural sciences, law, economics and communications. We have received quality, environmental and working environment certification.

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